INTERNATIONAL RECORD OF MEDICINE

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SYMPOSIUM ON CHLOROTHIAZIDE AND ITS DERIVATIVES

PART I

GUEST EDITOR—JOHN H. MOYER, M.D.

The Pharmacology of Chlorothiazide and Its Analogues — KARL H. BEYER AND JOHN E. BAER

The Physiology of Salt and Water Retention and the Use of Diuretics in Treatment — JOHN H. MOYER

Pharmacology and Potency Estimation of Chlorothiazide and Thiazide Derivatives — RALPH V. FORD

Pharmacology of the Thiazide Derivatives — MORTON FUCHS AND SANFORD MALLIN

The Use of Chlorothiazide and Hydrochlorothiazide in the Treatment of Congestive Heart Failure — ALBERT N. BREST

Chlorothiazide and Hydrochlorothiazide in the Treatment of Congestive Heart Failure — JOHN W. KEYES, GERALD M. BRENEMAN, AND HERNAN ALVAREZ, JR.

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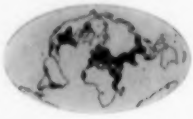

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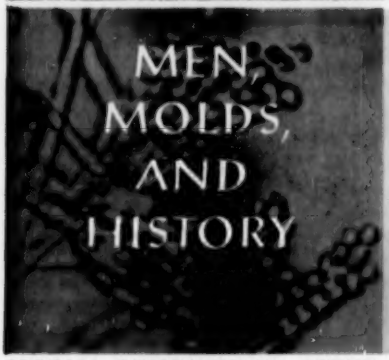

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Symposium on Chlorothiazide and Its Derivatives

Part I

GUEST EDITOR—JOHN H. MOYER, M.D.

The Pharmacology of Chlorothiazide and Its Analogues

Karl H. Beyer, M.D., and John E. Baer, Ph.D.

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Since the initial reports in 1957 on the chemical structure of chlorothiazide by Novello and Sprague[16] and the description of its saluretic action by Beyer et al,[6, 7] analogues of the compound have been synthesized in numerous laboratories. The widespread interest in these compounds is attributable to the unusual utility and safety of chlorothiazide in the management particularly of cardiovascular-renal diseases.[2-4]

The purpose of this report is to deal with the pharmacology of chlorothiazide and of its analogues that have been introduced to the medical profession, insofar as that knowledge is available to us or was determined in these laboratories up to the time this communication was prepared.

CHEMISTRY

The compounds presently available in this country and abroad include chlorothiazide,* hydrochlorothiazide,† their analogues wherein the chloro group is re-

Part II of this Symposium will appear in the September issue.

* The trade name of Merck Sharp & Dohme, Division of Merck & Co., Inc., for chlorothiazide, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, is Diuril in the United States and Canada, Saluric in the United Kingdom, Chlotride in Europe, the Near East, and the Far East, and Clotride in Latin America and Portugal.

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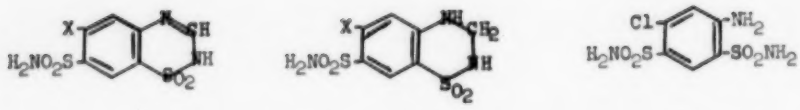

I II III

FIG. 1. Structural formulas of chlorothiazide and its analogues. *I*, X = Cl (chlorothiazide), X = CF_3 (flumethiazide); *II*, X = Cl (hydrochlorothiazide), X = CF_3 (hydroflumethiazide); *III*, chlorodisulfamylaniline.

placed by a trifluoromethyl substitution,* and chlorodisulfamylaniline,† which is both a precursor and a hydrolytic product of the chloro analogues in both series. The structures of these several compounds and their distinctions may be represented as shown in figure 1.

Except for chlorodisulfamylaniline, it may be seen that the available compounds are very similar in structure to the original chlorothiazide. In his discussion of the relation of structure to activity, Sprague[23] pointed out that the substitution of one halogen in the 6-position on the ring for another did not alter significantly either the potency or the qualitative character of the drug action. Indeed, the substitution of the trifluoromethyl pseudohalogen for the chloro group in either the chlorothiazide or hydrochlorothiazide series partakes of that generalization, as can be derived from the data to be presented herein. On the other hand, the saturation of the thiadiazine moiety is capable of increasing substantially the potency of the resulting compound in both the chloro and the trifluoromethyl series.

All of these compounds are acidic, and as such are but slightly soluble in water. However, they are readily soluble at *p*H greater than 7 and show no tendency to crystallize from body fluids when administered orally or parenterally in dosages considerably in excess of those employed in therapy. The benzothiadiazines can be hydrolyzed to yield the corresponding chloro or trifluoromethyl disulfamylaniline. This, in turn, can be diazotized and coupled with a chromogen for analytical purposes. Whereas chlorothiazide is more easily hydrolyzed under alkaline conditions,[1] hydrochlorothiazide undergoes hydrolysis more rapidly in a neutral medium.[7]

PHARMACOLOGY

Electrolytic Response. The patterns of electrolyte response for these several compounds are essentially similar. Whereas the earlier carbonic anhydrase inhibitor, acetazolamide,‡ induced predominantly an increase in the urinary elimination of sodium and bicarbonate,[14] these compounds tend to cause predominantly an increase in sodium and chloride elimination, thus their designation as saluretic agents. Like

* The trade name of E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corp., for flumethiazide, 6-trifluoromethyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, is Ademil. The trade name of Leo Pharmaceutical Products for hydroflumethiazide, 6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, is Rontyl.

† The trade name of Ferrosan for chlorodisulfamylaniline is Salamid.

‡ The trade name of Lederle Laboratories Division, American Cyanamid Co., for acetazolamide, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, is Diamox.

acetazolamide, all these several compounds produce about the same increase in potassium excretion when compared on the basis of saluretic potency. This generalization has been noted by the several investigators who have reported on these agents.

Typical renal clearance experiments illustrating the electrolyte excretory response to acetazolamide, chlorothiazide, hydrochlorothiazide, flumethiazide, and chlorodisulfamylaniline are represented in table I. None of the compounds significantly influences glomerular filtration rate at these dosages or as employed clinically. In these experiments urine flow gave no true indication of the diuretic propensity of the compounds. No attempt was made in these data to represent the comparative order of activity of these compounds, for this will be done under more suitable experimental conditions (figs. 2–6).

A slight difference in the chloruretic response between the unsaturated and the dihydro series can be illustrated by comparing the saluretic response with chlorothiazide and hydrochlorothiazide under conditions of ammonium chloride–induced acidosis or sodium bicarbonate–induced alkalosis in dogs (table II). Here it may be seen that a chloruretic response to hydrochlorothiazide is exaggerated moderately over that of chlorothiazide under conditions of acidosis. Under conditions of

TABLE I

Effect of Various Compounds on Electrolyte Excretion by Dogs*

		Sodium		Potassium	Chloride	Urine		
		Excretion, μEq./min.	% reabsorbed	Excretion, μEq./min.	Excretion, μEq./min.	pH	Flow, ml./min.	GFR, ml./min.
Acetazolamide	C	44	99.5	23	7	6.29	2.1	65.1
	D	183	97.9	83	30	7.57	5.4	61.7
Chlorothiazide	C	80	98.7	7	20	6.45	6.2	46.6
	D	462	92.3	22	282	7.37	4.0	43.3
Flumethiazide	C	62	99.1	18	—	6.88	2.5	46.4
	D	391	94.1	48	331	7.03	3.9	45.7
Hydrochlorothiazide	C	70	99.2	46	23	6.95	2.0	61.7
	D	719	93.3	89	608	7.17	6.3	74.3
Chlorodisulfamylaniline	C	5	99.9	9	6	5.86	4.5	64.2
	D	37	99.5	15	15	6.64	6.1	59.3

GFR = glomerular filtration rate, as measured by exogenous creatinine clearance. All values are averages of replicate 10-minute clearance periods in both the control phase (C) and the drug phase (D) of the experiment.

* 1.25 mg./Kg. prime, intravenous; 1.5 mg./Kg./hour.

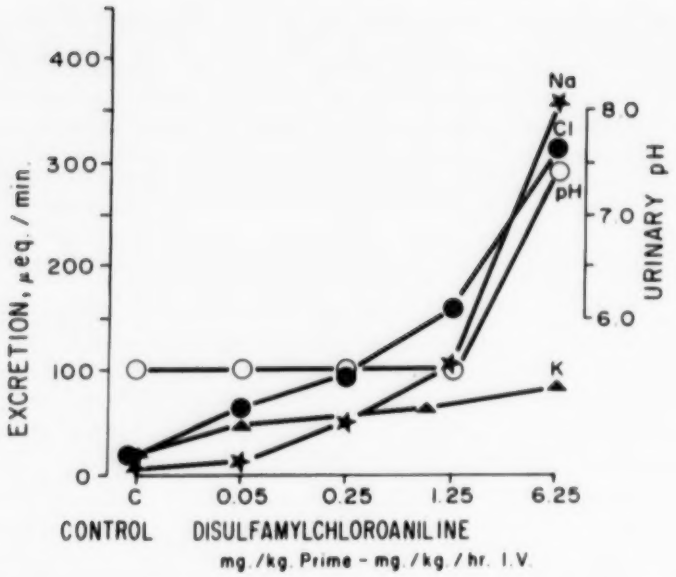

FIG. 2. Effect of increasing intravenous doses of 2,4-disulfamyl-5-chloroaniline on electrolyte excretion in dogs. A priming dose, as indicated was given and venoclysis begun at the indicated rate 20 minutes prior to replicate 10-minute clearance periods.

alkalosis, chlorothiazide tends to cause an increase in bicarbonate excretion to attend the chloruretic effect (table II). On the other hand, hydrochlorothiazide causes a more profound chloruresis even under conditions of marked alkalosis, there being relatively less effect on bicarbonate excretion. Moyer et al[15] have noted that in patients the chloruretic-to-natruretic response may be greater for hydrochlorothiazide than for chlorothiazide.

This modest difference between the chloruretic response to chlorothiazide or flumethiazide and their dihydro derivatives may be anticipated to produce clinical differences in patient response that may be of consequence. Thus, while the action of hydrochlorothiazide may more nearly simulate that of the organomercurials, one would expect it to have a greater propensity to induce a hypochloremic alkalosis than would be the case for chlorothiazide. This duality of chlorothiazide effectiveness with respect to the principal anion being excreted under conditions of alkalosis or acidosis might be thought to contribute in some measure to the maintenance of homeostasis.

Potency. The apparent potency of hydrochlorothiazide and its trifluoromethyl analogue is substantially greater than that of chlorothiazide or flumethiazide. The comparative potency of the several compounds varies somewhat from one species to another and from patient to patient. The order of potency and the pattern of electrolyte response for the dog can be illustrated by comparable data for these

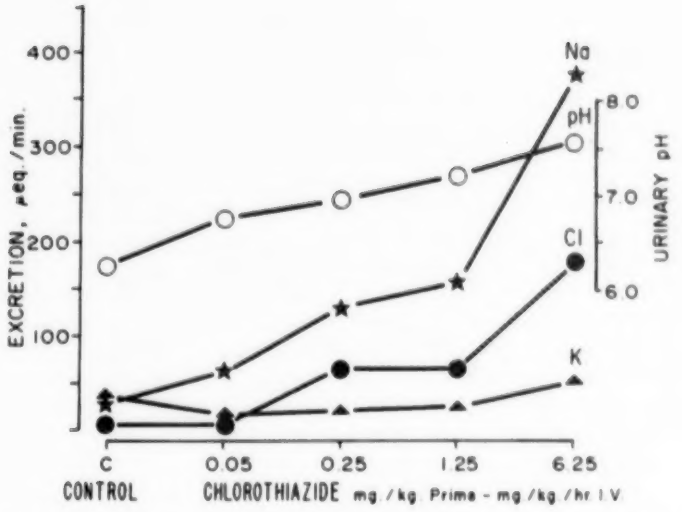

FIG. 3. Effect of increasing intravenous doses of chlorothiazide on electrolyte excretion in dogs.

several compounds when administered intravenously (figs. 2-6). These data are taken from renal clearance experiments where the intravenous dosage was increased after each duplicate period. A 20-minute period for equilibration was allowed after each increase in dosage before the next pair of clearances.

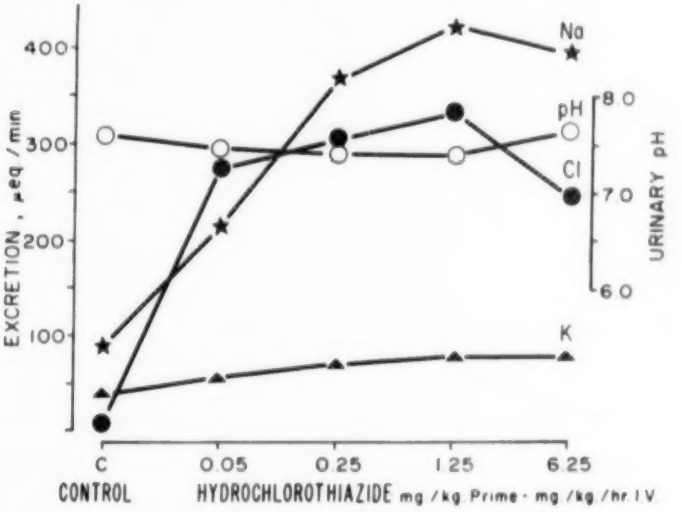

FIG. 4. Effect of increasing intravenous doses of hydrochlorothiazide on electrolyte excretion in dogs.

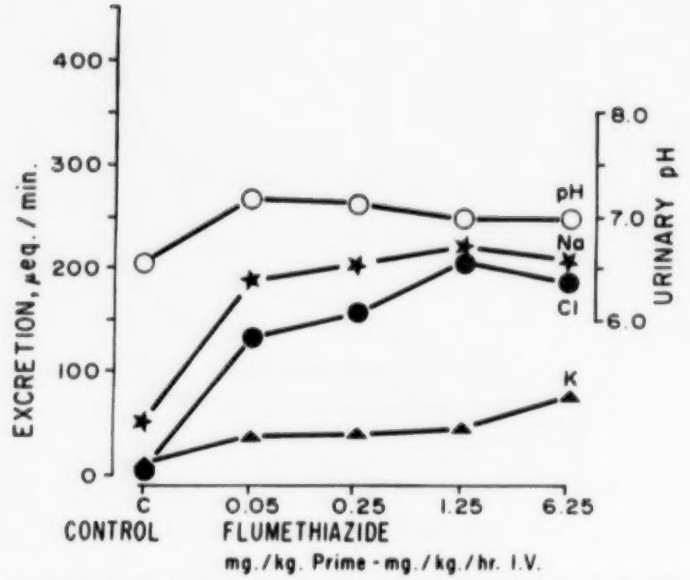

FIG. 5. Effect of increasing intravenous doses of flumethiazide on electrolyte excretion in dogs.

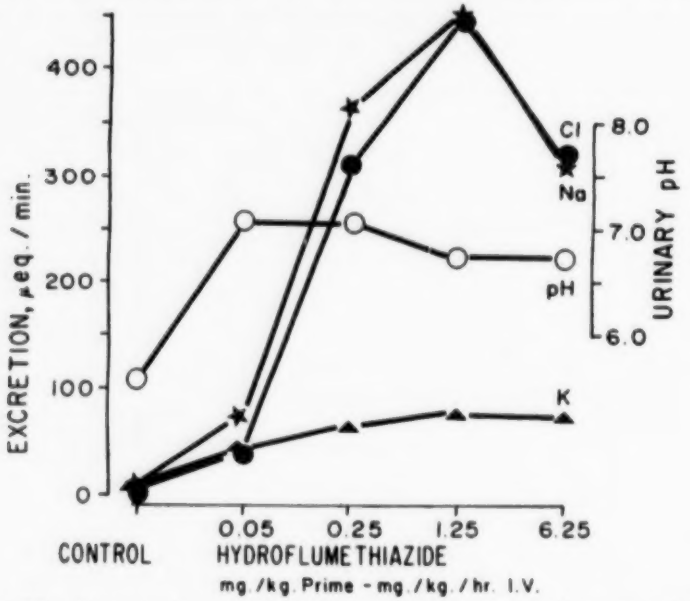

FIG. 6. Effect of increasing intravenous doses of hydroflumethiazide on electrolyte excretion in dogs.

The dosage response curve for flumethiazide was sufficiently flat, in our experience, as to make a comparison of potency hazardous. Judged by experiments such as were represented in table I, but employing a series of different dosages in several dogs, the absolute potency of flumethiazide is only slightly less than that of chlorothiazide. In general, we have found flumethiazide to be active at very low dosages but to have a comparatively flat slope to its dose-response curve. On the other hand, chlorothiazide yields a systematic increase in dosage response over the range tested. Tisch et al[28] have reported that in crossover experiments the oral saluretic efficacies of flumethiazide and chlorothiazide were about equal in the dog. (Compare figures 3 and 5.)

Recently, Baer et al[2] have compared the potency of hydrochlorothiazide with that of chlorothiazide in dogs. In their hands, the natruretic response to hydrochlorothiazide, administered orally, was 9.3 times that of chlorothiazide. These data agree with the previous report by de Stevens et al.[8] Similarly, Barrett et al[3] reported hydrochlorothiazide to be 6.3 to 8.0 times as active as chlorothiazide in the dog. They likewise pointed out the seemingly greater chloruretic-to-natruretic effect of

TABLE II

*Effect of Chlorothiazide and Hydrochlorothiazide on Electrolyte Excretion in Dogs Made Acidotic with Ammonium Chloride or Alkalotic with Sodium Bicarbonate**

		Sodium		Potassium	Chloride	Bicarbonate			
		Excretion, μEq./min.	% reabsorbed	Excretion, μEq./min.	Excretion, μEq./min.	Excretion, μEq./min.	Urine pH	GFR, ml./min.	Plasma pH
Ammonium chloride acidosis									
Chlorothiazide	C†	18	99.8	34	80	2	5.3	57.5	7.23
	D	200	97.5	53	320	6	4.7	57.1	
Hydrochlorothiazide	C	21	99.8	12	96	6	5.2	59.7	7.24
	D	289	96.1	63	437	6	4.7	51.2	
Sodium bicarbonate alkalosis									
Chlorothiazide	C	212	97.8	38	9	182	7.9	64.8	7.57
	D	598	92.8	78	194	415	8.0	55.5	
Hydrochlorothiazide	C	220	97.3	28	7	209	7.9	55.1	7.49
	D	727	92.8	142	316	389	7.8	68.1	

* Ammonium chloride or sodium bicarbonate was administered orally in a dosage of 100 mEq./day for five days.

† Average of triplicate successive 10-minute clearance periods. C = control phase. D = drug phase. Hydrochlorothiazide dosage: 0.25 mg./Kg. intravenous prime plus 0.3 mg./Kg./hour intravenous. Chlorothiazide dosage: 2.5 mg./Kg. intravenous prime plus 3.0 mg./Kg./hour intravenous (according to Baer et al[2]).

hydrochlorothiazide than of chlorothiazide. In the rat, hydrochlorothiazide was reported by Renzi et al[20] to be 7 to 21 times as potent as chlorothiazide. The figure of 10 times greater potency in the rat reported by Goldberg and Hwang[12] is in agreement with the findings of Renzi et al.[20] (Compare figures 3 and 4.)

We have found the trifluoromethyl analogue of hydrochlorothiazide to be discernibly less potent than hydrochlorothiazide at submaximally effective dosages (figs. 2–6). There are no other comparisons of potency between hydrochlorothiazide and its corresponding hydroflumethiazide in the literature to date. However, Kobinger and Lund[13] have reported hydroflumethiazide to be 15 to 20 times as potent on a dosage basis as chlorothiazide in the rat. Tisch et al[25] reported that hydroflumethiazide was only about twice as potent as flumethiazide and chlorothiazide when assayed in the dog.

There is one interesting difference between the dose-response curves for chlorothiazide and perhaps flumethiazide as compared to those of their hydrogenated analogues. It will be noted that in the intravenous dose-response curves for hydrochlorothiazide and hydroflumethiazide (figs. 3–6), there was a depression of sodium and chloride excretion at supramaximally effective dosages. This interesting observation is not attributable to a depression in glomerular filtration rate but to an absolute increase in the reabsorption of sodium. This same depression in the excretion of electrolytes was noted by Moyer et al[15] in man for hydrochlorothiazide at supramaximal dosages, although it was not commented on by Ford.[11] It should be noted, also, that both sodium and chloride reabsorption was depressed at the highest dosage, but the kaluretic effect was not influenced similarly.

The natruretic effect of chlorodisulfamylaniline is substantially less than that of chlorothiazide or any of the other compounds. However, the kaluretic effect was as great as those of the other agents. The compound is well absorbed and is demonstrably active when administered orally at a dosage of 3.0 mg./Kg. It has neither the advantage of potency nor an attractively different electrolyte pattern to commend it. (See figure 2.)

The maximal saluretic responses for these several compounds administered orally at supramaximally effective dosages are essentially similar, insofar as this has been studied. This is particularly evident when the oral dose-response curves for chlorothiazide and hydrochlorothiazide are compared, as in figure 7. From the regression curves, it can be calculated that the submaximal natruretic potency of hydrochlorothiazide was 9.3 times that of chlorothiazide. However, at maximally effective dosages, the six-hour natruretic response to chlorothiazide was at least as great as that of hydrochlorothiazide. From these considerations it might be projected that if the dosage of chlorothiazide or hydrochlorothiazide were individualized to the patient, it should be possible to elicit essentially the same clinical response to either agent. In other words, adjustment of dosage of two essentially similarly acting compounds should yield a similar maximal renotropic effect, should this be desired in clinical practice.

Mode of Renotropic Action. The modes of renotropic action of these several compounds appear to be similar. They can be demonstrated to inhibit carbonic anhydrase in vitro, presumably by virtue of their free sulfamyl group. However, they

do differ quantitatively in their order of activity. We have listed our own data for the several compounds in table III. Chlorothiazide is 1/10 to 1/14 as potent as acetazolamide. In turn, hydrochlorothiazide is 1/10 as potent as chlorothiazide. Saturation of the double bond in the flumethiazide series likewise decreases the carbonic anhydrase inhibitory potency by a factor of 10. Both of the trifluoromethyl compounds are weaker inhibitors of carbonic anhydrase than are the chloro analogues.

The fact that hydrochlorothiazide is a more potent saluretic agent in vivo and a less active carbonic anhydrase inhibitor in vitro than chlorothiazide has lent some support to the supposition that the saluretic effect of these agents may be dissociated from their ability to inhibit that enzyme. On the other hand, the decreased in vitro activity is not reflected in either an increase or an appreciable decrease in saluretic potency as the chlorine atom is replaced by a trifluoromethyl group. Certainly, these seeming differences in degree of carbonic anhydrase inhibitory activity cannot be considered to qualify a difference in the mode of action of hydrochlorothiazide and chlorothiazide or their trifluoromethyl analogues, in our opinion.

The modes of diuretic action of these several agents, including the chlorodisulfamylaniline analogue, appear to be basically the same. Such difference in chloruresis as may obtain between the dihydrobenzothiadiazines and the benzothiadiazine series is more probably related to differences in the back diffusion of chloride and bicarbonate secondary to differences in the distribution of the drugs, rather than to real differences in their mode of action. Thus, their effects seem to be additive, insofar as they have been studied, in that the maximal natruretic response to two or more of these compounds administered together is essentially the same as could be expected from a maximal response to any one of the several agents. These experiments will be reported in full elsewhere. Pitts et al,[18] Ford,[19] and Beyer[8] have pre-

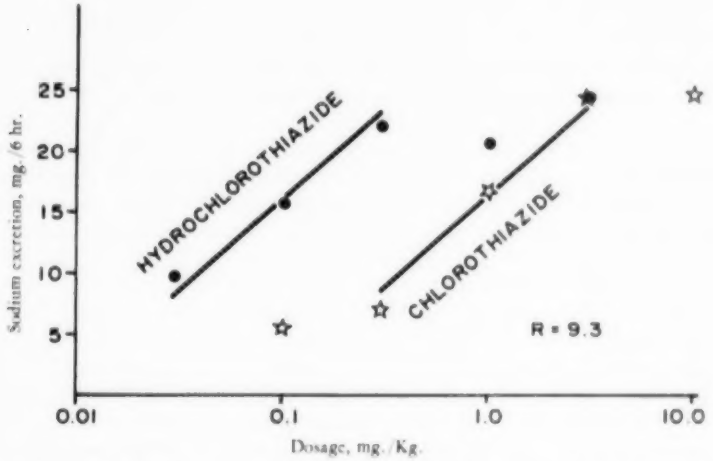

FIG. 7. Relative oral natruretic potency of hydrochlorothiazide and chlorothiazide in dogs. Each point represents at least 5 dogs; relative potency by analysis of variance, 9.3.

TABLE III

In Vitro Carbonic Anhydrase Inhibitory Activity*

	Molarity to cause 50% inhibition
Chlorothiazide	1.7×10^{-6}
Flumethiazide	4.2×10^{-6}
Hydrochlorothiazide	2.3×10^{-6}
Hydroflumethiazide	1.7×10^{-6}
2,4-Disulfamyl-5-chloroaniline	3.5×10^{-6}

* Procedure of Philpot and Philpot.[17]

sented data from which it may be concluded that the mode of action of the chlorothiazide analogues and that of the organomercurials are dissimilar.

Antihypertensive Response. The antihypertensive response to chlorothiazide and its analogues appears to be attributable to their effect on electrolyte excretion or distribution. Whether or not there is an extrarenal basis for the action of any of these agents is not firmly established, although there is some evidence to support such a belief. Dustan et al[9] are of the opinion that the antihypertensive effect of chlorothiazide is due to the reduction in circulating blood volume that attends the diuretic response to the agent. They believe that a reduction of blood volume, as induced by chlorothiazide diuresis, stimulates vasomotor tonus. They consider that under these circumstances of oligemic intensification of vasomotor tonus, the response to antihypertensive agents that influence adrenergic mediation of vasomotion is facilitated (i.e., ganglionic blocking agents, reserpine, hydralazine, and monoamine-oxidase inhibitors).

It is possible that chlorothiazide influences, either directly or indirectly (secondary to saluresis), the distribution of sodium and potassium ions on the two sides of the cell membrane of particularly the arteriolar smooth muscle. If this were true, it could alter the responsiveness of the muscle to adrenergic stimuli. Beavers and Blackmore[4] and Preziosi et al[19] have reported that large dosages of chlorothiazide administered to experimental animals decreased the response to the intravenous administration of epinephrine and norepinephrine. In addition, Barrett et al[3] have shown that hydrochlorothiazide, administered intravenously in substantial amounts, increases slightly the depressor response to hydralazine and to histamine.

Regardless of the mode of action, it seems clear that chlorothiazide and its congeners are quite capable of lowering blood pressure in many hypertensive persons and of increasing the efficacy of most other types of antihypertensive therapy.

Acute Toxicity. The acute toxicity of all these compounds is so low as not to be a factor in the determination of their safety. Thus, if suspensions of chlorothiazide, hydrochlorothiazide, or their trifluoromethyl analogues are employed, one cannot give sufficient amounts of the compounds orally to determine an LD_{50} (a calculated lethal dose for 50 per cent of the animals employed). There is some difference in the acute toxicity values for specific compounds reported by several investigators. This difference in absolute values has risen by virtue of technical factors involved in the determination of such values.

In table IV we have presented the acute intravenous toxicity of the sodium salt in aqueous solution for each of the several compounds prepared and handled under identical conditions. While there are absolute differences in the acute toxicity, all of the compounds have such a high order of LD_{50} values that they cannot be approached under clinical conditions.

The "toxicity" of these agents, as seen under conditions of clinical use, has to do with their overt pharmacodynamic effect on electrolyte balance, insofar as is known. If these compounds are employed without due regard for the effects that they are called on to induce, they can cause hypokalemia and, less frequently, hypochloremic alkalosis. Under unusual conditions, the compounds may produce a hyponatremia.

Chlorothiazide has been unusually free clinically of toxicity or side effects of the compound, per se. It is too early to be assured that the pattern of safety of the several other agents will be the same. The chlorodisulfamylaniline could conceivably have a greater propensity to induce allergic hypersensitivity due to the free amino group on the aromatic ring moiety. Although the trifluoromethyl group is chemically stable, it will take some time before it can be established with certainty that on chronic administration under clinical conditions, it will be similarly stable metabolically.

Metabolic Disposition. The metabolic disposition of chlorothiazide[1] and hydrochlorothiazide[2] is better understood than that of the trifluoromethyl analogues. All of these compounds are well absorbed after oral administration. Their volume of distribution and distribution by tissues is such that they have little propensity to induce any side effects or pharmacodynamic actions other than the renotropic effect on electrolyte excretion.

After intravenous administration, both chlorothiazide and hydrochlorothiazide are essentially completely excreted in the urine in a matter of a few hours. Urinary recovery after oral administration of either drug to laboratory animals is 40 to 60 per cent, but unchanged drug is excreted in the feces only after tremendous oral doses. The urinary recovery after oral administration of low doses of hydrochlorothiazide to rats is 40 to 60 per cent, as determined with tritiated hydrochlorothiazide.[22]

It would appear that the volume of distribution of hydrochlorothiazide is somewhat greater than for chlorothiazide and that its disposition acutely is almost entirely by way of the kidney. These points can be deduced from figure 8, wherein

TABLE IV

Acute Toxicity in Mice, Administered in Solution as the Sodium Salt

	Intravenous LD_{50}, mg./Kg.
Chlorothiazide	1120 (1040–1200)*
Flumethiazide	882 (803– 969)
Hydrochlorothiazide	884 (787– 993)
Hydroflumethiazide	643 (580– 712)
2,4-Disulfamyl-5-chloroaniline	735 (667– 810)

* Ninety-five per cent confidence limits.

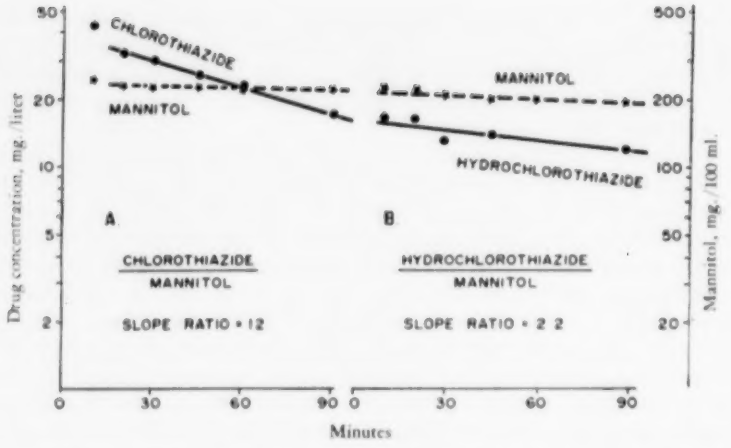

FIG. 8. Plasma levels after single intravenous dose of 10 mg./Kg. of (A) chlorothiazide and (B) hydrochlorothiazide to nephrectomized dogs. Mannitol (500 mg./Kg.) was used as the reference compound. Slopes (log concentration/time) were (A) chlorothiazide, 0.94; mannitol, 0.07; (B) hydrochlorothiazide, 0.28; mannitol, 0.13.

its falling plasma curve in a nephrectomized dog is compared to that for chlorothiazide in a similar preparation. It will be noted that the absolute value for the plasma concentration after administration of 10 mg./Kg. doses of the two compounds is lower for hydrochlorothiazide. On the other hand, the slope of the chlorothiazide curve is much greater, reflecting the greater hepatic elimination of the latter compound.

The renal clearances of hydrochlorothiazide and chlorothiazide are essentially the same, both compounds being rapidly secreted by the renal tubules in addition to their clearance by way of glomerular filtration. It is difficult to ascertain from presently available data whether there is a real difference in the duration of action of chlorothiazide and hydrochlorothiazide. Such comparisons as have been made by Barrett et al[3] indicate a longer duration of action when hydrochlorothiazide was administered to dogs at the same absolute dosage as for chlorothiazide. They provided no data that would permit one to determine the relative duration of action of the two compounds when administered at equally potent dosages. However, if the volume of distribution for hydrochlorothiazide is greater than for chlorothiazide, as the data of Sheppard et al[22] and our own (fig. 8) indicate, hydrochlorothiazide may have a slightly longer duration of action due to its rate of redistribution.

In studies of the urine of animals receiving chlorothiazide, we have not been able to demonstrate any degradation products or any conversion to hydrochlorothiazide such as was suggested, but not demonstrated, by Richterich.[21] On the other hand, it is possible to demonstrate the presence of chlorodisulfamylaniline in the urine of patients or dogs that have received hydrochlorothiazide.

The trifluoromethyl group is relatively new to pharmacology. Its pharmacody-

namic equivalence to other halogen substitutions is well established in these benzothiadiazine analogues. No metabolic studies on the trifluoromethyl group have been reported in the literature; it might be presumed to have the same stability characteristics in man that it has in the chemical laboratory.

SUMMARY

In general, the pharmacology of chlorothiazide and its available analogues represents differences in degree rather than kind. Although the maximal renotropic effects of these agents are essentially the same, wherein they have been studied carefully, their increasing order of "potency" may be represented as chlorodisulfamylaniline, flumethiazide, chlorothiazide, dihydroflumethiazide, dihydrochlorothiazide.

Like chlorothiazide, all these agents increase the renal excretion of sodium and chloride predominantly. Their lesser kaluretic effect does not differ importantly with each drug. They are well absorbed when administered orally, they are fairly rapidly excreted by the kidney, and their distribution in the body is such as to minimize side effects that might otherwise be anticipated from their in vitro carbonic anhydrase inhibitory effects.

Chlorothiazide has been so widely employed in general practice as to have established a remarkable record for safety. The most frequent noteworthy side effects of it or of the less well-established compounds are attributable to the overt renotropic effects of these agents.

BIBLIOGRAPHY

1. Baer, J. E.; Leidy, L.; Brooks, A. V., and Beyer, K. H.: The physiological disposition of chlorothiazide (Diuril) in the dog, J. Pharmacol. & Exper. Therap. *125*:295–302, 1959.
2. Baer, J. E.; Russo, H. F., and Beyer, K. H.: Saluretic activity of hydrochlorothiazide (6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide) in the dog, Proc. Soc. Exper. Biol. & Med. *100*:442–446, 1959.
3. Barrett, W. E.; Rutledge, R. A.; Sheppard, H., and Plummer, A. J.: The pharmacology of hydrochlorothiazide (Esidrix™), a new, potent, orally effective sulfonamide diuretic, Toxicol. & Appl. Pharmacol. In press, 1959.
4. Beavers, W. R., and Blackmore, W. P.: Effect of chlorothiazide on vascular reactivity, Proc. Soc. Exper. Biol. & Med. *98*:133–135, 1958.
5. Beyer, K. H.: The mechanism of action of chlorothiazide, Ann. New York Acad. Sc. *71*:363–379, 1958.
6. Beyer, K. H.; Baer, J. E.; Russo, H. F., and Haimbach, A. S.: Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide): the enhancement of sodium chloride excretion, Fed. Proc. *16*:282, 1957.
7. Beyer, K. H., Jr.; Baer, J. E.; Russo, H. F., and Noll, R.: Electrolyte excretion as influenced by chlorothiazide, Science *127*:146–147, 1958.
8. de Stevens, G.; Werner, L. H.; Halamandaris, A., and Ricca, S., Jr.: Dihydrobenzothiadiazine dioxides with potent diuretic effect, Experientia *14*:463, 1958.
9. Dustan, H. P.; Cumming, G. R.; Corcoran, A. C., and Page, I. H.: A mechanism of chlorothiazide-enhanced effectiveness of antihypertensive ganglioplegic drugs, Circulation *19*:360–365, 1959.
10. Ford, R. V.: Mechanisms of action of diuretics as revealed by potentiation studies, J. Lab. & Clin. Med. *50*:814, 1957.
11. Ford, R. V.: The clinical pharmacology of hydrochlorothiazide, South. M. J. *52*:40–45, 1959.
12. Goldberg, M. E., and Hwang, K.: A study of the diuretic effect of dihydrochlorothiazide and its analogues in the rat, Fed. Proc. *18*:396, 1959.

13. Kobinger, W., and Lund, F. J.: Investigations into a new oral diuretic, Rontyl (6-trifluoromethyl, 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide), Acta pharmacol. et toxicol. *15*:265–274, 1959.
14. Maren, T. H.; Mayer, E., and Wadsworth, B. C.: Carbonic anhydrase inhibition. I. The pharmacology of Diamox, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, Bull. Johns Hopkins Hosp. *95*:199–243, 1954.
15. Moyer, J. H.; Fuchs, M.; Irie, S., and Bodi, T.: Some observations on the pharmacology of hydrochlorothiazide, Am. J. Cardiol. *3*:113–117, 1959.
16. Novello, F. C., and Sprague, J. M.: Benzothiadiazine dioxides as novel diuretics, J. Am. Chem. Soc. *79*:2028, 1957.
17. Philpot, F. J., and Philpot, J. St. L.: A modified colorimetric estimation of carbonic anhydrase, Biochem. J. *34*:1163, 1936.
18. Pitts, R. F.; Kruck, F.; Lozano, R.; Taylor, D. W.; Heidenreich, O. P. A., and Kessler, R. H.: Studies on the mechanism of diuretic action of chlorothiazide, J. Pharmacol. & Exper. Therap. *123*:89–97, 1958.
19. Preziosi, P.; Bianchi, A.; Loscalzo, B., and De Schaepdryver, A. F.: On the pharmacology of chlorothiazide, Arch. internat. de pharmacodyn. et de thérap. *118*:467–495, 1959.
20. Renzi, A. A.; Godoy, M.; Stein, M., and Ulsamer, G.: Diuretic activity of hydrochlorothiazide in the rat, Fed. Proc. *18*:436, 1959.
21. Richterich, R.: Natriuretic potency of hydrochlorothiazide in humans, Experientia *14*:458, 1958.
22. Sheppard, H.; Bowen, N. R.; Mowles, T. F., and Plummer, A. J.: Synthesis and biological disposition of hydrochlorothiazide-H^3, Fed. Proc. *18*:444, 1959.
23. Sprague, J. M.: The chemistry of diuretics, Ann. New York Acad. Sc. *71*:328–343, 1958.
24. Taggart, J. V. (consulting editor): Chlorothiazide and other diuretic agents, Ann. New York Acad. Sc. *71*:321–478, 1958.
25. Tisch, D. E.; Hoekstra, J. B., and Pindell, M. H.: Pharmacology of two new oral diuretic agents: 7-sulfamyl-6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide (BL-H320), and 7-sulfamyl-6-trifluoromethyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (BL-H346), Fed. Proc. *18*:451, 1959.

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The Physiology of Salt and Water Retention and the Use of Diuretics in Treatment

John H. Moyer, M.D.

PROFESSOR OF MEDICINE,
HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
PHILADELPHIA, PA.

Numerous disease syndromes are associated with abnormal salt and water retention by the kidneys. Compounds that block renal tubular reabsorption of salt and water reverse this process and improve symptoms associated with these syndromes. It is the purpose of this communication to review pertinent factors related to the use of diuretics in the therapy of numerous diseases.

PHYSIOLOGY OF WATER AND ELECTROLYTES

The renal regulation of water excretion takes place on a background of interrelationships with metabolism of sodium and other electrolytes. Alterations in sodium excretion have a marked effect on water excretion, and vice versa. It would appear that the primary stimulant to sodium excretory regulation arises in the extracellular fluid volume.

Probably the most universal concept of body fluid distribution is the product of the hypothesis of *milieu intérieur* of Claude Bernard and the hypothesis of homeostasis of Walter Cannon. The concept thus indicates that the cell is bathed in the extracellular fluid that acts as the environment of the cell. The plasma fluid in turn is, for practical purposes, extracellular fluid in contact with fluid-conservation mechanisms. Thus, the extracellular electrolytes are the same as in the plasma. This concept usually considers a more or less static state of equilibrium between the intracellular fluid and the extracellular space. Such a concept appears now to be quite erroneous, and as we gain additional information, it appears that there is a very kinetic and continuous exchange of fluids and electrolytes between the intracellular and the extracellular spaces. For example, a patient with ascites may completely exchange the ascitic fluid five or six times a day.

It appears that the adrenal corticoids not only affect the kidneys but also have a direct effect on the exchange of water and electrolytes between the intracellular phase and the extracellular phase. This process is brought about by alteration of metabolic activity of the cell. However, the primary response in water exchange between these phases is secondary to electrolyte shift, and the concentrations in the extracellular phase are largely regulated by the kidney. Thus the body can be looked on as a continuous fluid medium in which two principle constituents of solutes can be discerned: an intracellular phase and an extracellular phase separated by a semipermeable cell membrane through which fluid and electrolytes continually migrate. The composition of the extracellular phase remains rather uniform, consisting mostly of sodium cations balanced by chloride and bicarbonate. The intracellular fluid composition varies somewhat from time to time but contains primarily potassium, sodium, and magnesium cations balanced by phosphate, chloride, and protein anions.

Solutes that traverse cell membranes freely elevate the osmotic pressure on both sides of the membrane equally and hence cannot promote any transfer of water. For example, the total osmotic pressure of the extracellular fluid may be greatly increased owing to the accumulation of large amounts of urea, but no exchange of water between cells and extracellular fluid occurs because urea can diffuse through cell membranes without restraint. In contrast, substances that do not penetrate cell membranes freely and are concentrated on the extracellular side of the cell membrane elevate the osmotic pressure on one side of the membrane only, and thereby determine the distribution of water across it. Potassium is concentrated in the intracellular phase and sodium is concentrated in the extracellular phase. Such poorly diffusible solutes are said to exert an effective osmotic pressure. By contrast to solute composition at equilibrium, the osmotic pressure appears to be similar in the intracellular and the extracellular phases due to free migration of water across the membrane until a state of osmotic equilibrium is attained.

If the effective osmotic pressure of extracellular fluid rises because of the addition of sodium salts, water will be withdrawn from cells, causing their volume to contract and their osmotic pressure to rise; at the same time, the volume of extracellular fluid will expand and its osmotic pressure will fall until a state of equilibrium is reached. Similarly, if sodium salts are removed from the extracellular fluid, water will move into cells, expanding their volume and lowering their osmotic pressure. Thus the osmotic pressure of the extracellular compartment will rise and its volume will fall. In both instances, the transfer of water will stop when osmotic uniformity has been re-established.

The kidneys are largely responsible for maintaining the volume and composition of body fluids. There are several coordinated mechanisms responsible for this renal regulation.

Water Balance. The maintenance of a nearly constant volume of water in the several fluid compartments of the body is largely controlled by the antidiuretic hormone (ADH), but other hormones are also involved. Available evidence indicates that most of the glomerular filtrate is returned to the peritubular blood from the proximal tubules by simple diffusion. More than 99 per cent of the remainder of the filtered water may be reabsorbed in the distal tubule by an active process. This latter mechanism makes it possible for the kidney to return water to the circulating blood against an osmotic gradient and requires ADH to function.

The secretion of ADH is regulated by changes in concentration of sodium chloride in the extracellular fluid and therefore in the plasma. Osmoreceptors are located in certain of the blood vessels supplying the brain. Hydration of sufficient degree to reduce only slightly the plasma sodium chloride causes the osmoreceptors to swell, which reduces the output of ADH. This results in an increased output of water with little change in salt excretion. The extra water is thus eliminated. Under normal conditions, water intake usually exceeds requirements and a balance is maintained by renal excretion of the surplus. The renal re-establishment of an isotonic plasma after excessive water intake is then largely due to the functional linkage between the neurohypophysis and the kidneys.

During a period of dehydration, a converse chain of events takes place. If water

is withheld, the extracellular fluid becomes hypertonic since water is lost through the urine, lungs, and skin without a parallel salt loss. The osmoreceptors respond by stimulating the neurohypophysis to secrete increased amounts of ADH. As this hormone accumulates in the cells of the renal tubules, the kidneys conserve water by secreting a more concentrated urine. However, compensation cannot be effected during water deprivation because unavoidable water losses continue through the skin, lungs, and the minimum urine volume necessary to excrete waste products.

Electrolyte Balance. Normally, sodium chloride balance is maintained by the kidneys in a manner similar to the maintenance of water balance. Average daily intake exceeds requirements and the excess is excreted in the urine. The body conserves salt much more efficiently than water. We have seen that if neither food nor water is ingested, water depletion is the dominant picture. If water alone is administered, it requires a considerable period of time in the absence of abnormal salt loss before serious depletion occurs. The kidneys practically cease to excrete salt under these conditions. To maintain a constant sodium chloride concentration in the extracellular fluid requires that the urine may sometimes contain more than, less than, or an equivalent amount of salt as the plasma.

Of the sodium present in the glomerular filtrate, about 85 per cent is said to be reabsorbed by the cells of the proximal tubule. Since a similar amount of water is absorbed by this segment of the nephron, the fluid of the proximal tubule is thought to remain isotonic or slightly hypotonic. The glomerular filtrate is presumably a fluid of the same electrolyte composition as extracellular fluid, which is in equilibrium with cell fluid. Because of the absence of a favorable osmotic gradient, it may be inferred that the transfer of sodium from tubular fluid to the tubule cells in the proximal tubule is an active process involving the expenditure of energy. Water then follows passively due to osmotic pressure difference between intratubular and peritubular fluids, which have been established by prior reabsorption of solutes. In the distal tubule, active reabsorption of water occurs under the influence of ADH. There are also proponents of the theory that a mechanism exists for the active reabsorption of sodium activated by adrenal cortical steroids in this segment. Some confusion has been created by the extensive studies with desoxycorticosterone, a synthetic compound that probably has no physiological counterpart. One important difference between desoxycorticosterone and adrenal cortical extract is that the former is salt-retaining at all levels of plasma sodium. On the other hand, cortical extracts are salt-retaining at low plasma levels of sodium, but may actually increase the output of salt when the plasma sodium concentration is elevated.

Recently, work has indicated the existence of ion-exchange mechanism in the cells of the renal tubules that are involved in the reabsorption of sodium. Hydrogen, potassium, and ammonium ions are believed to be secreted into the tubule lumen in exchange for sodium ions. The location in the nephron and the control of these exchange mechanisms have not been established.

The recent discovery that the adrenal venous blood of mammals contains a steroid that is many times more potent than desoxycorticosterone in controlling renal electrolyte excretion resulted in the isolation and identification of aldosterone. It is approximately 30 times more potent than desoxycorticosterone as a salt-retaining

hormone. Although hydrocortisone may be present in larger amounts in adrenal venous blood of dog and man, aldosterone has a dominant action on electrolyte excretion because of its greater potency. There is evidence to indicate that its secretion varies according to requirements for electrolyte balance. In normal men, sodium restriction increases the output of hormone and reduces urine sodium. After resumption of a normal sodium intake, the excretions of both hormone and sodium return to control levels.

Although the mechanism that controls the release of aldosterone is uncertain, the concentration of sodium in the extracellular fluid, the concentration of potassium, and blood volume have all been implicated. Unlike the other cortical steroids, the release of aldosterone appears to be independent of corticotropin (ACTH).

It is commonly stated that the cortical hormones and ACTH, through its influence on cortical hormone secretion, cause a renal retention of sodium and water and a loss of potassium. Actually, these hormones may decrease the elevated plasma potassium level after adrenalectomy of animals without increasing urinary excretion of this ion. Such observations indicate that cellular shifts of potassium as well as a decreased rate of excretion are involved in the hyperkalemia of adrenal insufficiency. Nevertheless, cortical hormones are effective in promoting potassium excretion and may even produce hypokalemia.

The Effect of Renal Hemodynamics on Sodium Excretion. Interest in the relationship of hemodynamic factors on sodium and water excretion was aroused by the postulate that sodium retention in edema of heart failure may result from a decrease in cardiac output. This in turn would reduce renal blood flow and glomerular filtration rate. The lower volume of filtrate and hence sodium presented to the tubules under these conditions was thought to result in more complete reabsorption. There is ample evidence that acute reductions in blood pressure may be associated with a decrease in glomerular filtration rate, urine volume, and sodium excretion, in both animals and man. These changes occur from hemorrhage or drug-induced hypotension. Conversely, elevation of blood pressure from a hypotensive to a normotensive level by infusion of a vasoconstrictor agent usually results in improvement in renal functions, including the rate of water and sodium excretion.

These results should not be taken to indicate that change in glomerular filtration rate is an important regulatory mechanism for sodium and water excretion. On the contrary, changes in active reabsorption of water and sodium in the renal tubules appear to be the important mechanisms for maintaining a constant volume and composition of body fluids. Conditions associated with a chronic reduction in glomerular filtration rate, such as hypophysectomy in dogs and various causes in man, are not necessarily associated with an abnormal fluid and electrolyte balance.

It is quite obvious that compounds that block reabsorption of sodium and other electrolytes in the renal tubules will be the most effective agents for treating the various syndromes associated with edema due to salt and water retention. This is the place of diuretic therapy!

DIURETIC THERAPY

Diuretic agents, as important as they may be, are only one aspect of the treatment

of patients with abnormal sodium and water retention. The use of diuretics is not a curative measure, but rather these agents improve only the symptoms associated with edema formation. Consequently, when possible, the basic physiological defect should be corrected. With the advent of potent and safe diuretics, attention has been directed more and more toward the defective excretion of sodium. Since renal retention of sodium and water is a secondary effect, therapy should be aimed at the primary disease when this is possible. Diuretics are indicated when these more direct measures fail.

Collateral Therapy. In advanced cardiac failure, exercise reduces the glomerular filtration rate below a critical level and this may contribute to the renal retention of sodium and water. Increasing the glomerular filtration rate or reducing tubular reabsorption of sodium and water will correct this tendency toward fluid accumulation. Some improvement in renal functions may occur with bed rest. Glomerular filtration rate is highest when the patient is supine and decreases as the upright position is assumed. Continued exercise tends to produce a progressive reduction in glomerular filtration. Aside from reducing the burden on the heart, the improvement in renal function frequently observed during bed rest is a valuable therapeutic adjunct for patients in heart failure. In noncardiac edema, complete bed rest is rarely indicated.

Bed rest for the treatment of heart failure should be viewed as a temporary measure only, since many secondary physiological alterations follow prolonged bed confinement. Nevertheless, restricted physical activity should be advised as a permanent measure. Once heart failure has developed, it is rare that cardiac function returns entirely to normal, irrespective of the etiology of the disease or the therapeutic program instituted. Moreover, the more frequently and more severely a patient decompensates, the more difficult it is to improve cardiac function to a condition even approaching normal.

Sodium chloride intake should also be given primary consideration in patients with edema. Water intake is of little importance so long as sodium intake is rigidly restricted. In fact, a large urinary volume tends to promote an increase in sodium excretion. When a patient has had a low salt intake for a period of time, the body becomes relatively depleted of sodium. Consequently such patients are quite vulnerable to excessive sodium loss such as may occur in diarrhea or vomiting.

Potassium deficiency is another complication of diuretic therapy. Digitalis toxicity may be precipitated by hypokalemia. Clinically, extreme muscle weakness, cardiac irregularities, and abdominal distention are clues that should lead to the diagnosis. Should potassium deficiency occur, oral potassium chloride in a dosage of 2 to 5 Gm. daily is indicated.

SUMMARY OF DIURETIC THERAPY FOR SPECIFIC DISEASE ENTITIES

Congestive Heart Failure. Since the primary defect in congestive heart failure is inadequate cardiac output, every effort should be made to restrict the patient's activities. The judicious use of a cardiac glycoside is indicated before a diuretic is given.

Diuretics may be employed as follows:

1. A parenteral mercurial diuretic should be given initially when heart failure is severe, e.g., meralluride, 2 cc. intramuscularly, or mercaptomerin, 2 cc. subcutaneously, daily for three to five days until gross edema has disappeared.

2. Chlorothiazide,* 1000 mg., may be given every 8 to 12 hours after the emergency is controlled. The dosage is gradually decreased to the minimally effective dosage that will control the edema, but no less than 250 mg. daily should be given.

3. Chlormerodrin, 4 to 8 tablets daily, may be given for maintenance of the edema-free state if the response to chlorothiazide is not adequate.

4. When heart failure is mild, compensation may also be maintained with acetazolamide or ethoxzolamide, 250 mg. daily for three consecutive days of each week. In moderate to severe heart failure, acetazolamide (or ethoxzolamide) will rarely be adequate for maintenance therapy. Chlorothiazide (500 to 1000 mg. twice daily) or chlormerodrin (1 to 2 tablets after each meal and at bedtime) must be used if the oral route of drug administration is to be employed in such cases. Otherwise, parenterally administered mercurial agents must be given in adequate dosage (1 to 4 cc.) and as frequently as necessary to maintain the edema-free state and full cardiac compensation.

Premenstrual Edema. Edema is not marked in this condition but the symptoms may be annoying. The following prophylactic treatment may be used: On the last five to seven days of the menstrual cycle, with the onset of subjective tension, place the patient on a low-sodium diet. Also administer chlorothiazide in a dosage of 500 mg. twice a day (or hydrochlorothiazide in appropriate dosage), or 250 mg. of acetazolamide (1 tablet) daily, or 4 to 8 tablets of chlormerodrin daily.

Edema of Pregnancy. Since pre-existing disease may be responsible for edema in this condition, a close medical survey must be completed. Therapy may be summarized as follows: (1) At first sign of edema, place the patient on a low-sodium diet. (2) If edema is not controlled by diet alone, administer 4 to 8 tablets of chlormerodrin daily or chlorothiazide, 500 mg. twice daily (or hydrochlorothiazide in appropriate dosage), or 250 mg. of acetazolamide every other day if edema is not marked.

Nephrotic Syndrome. Multiple factors are operative in this condition and include excessive urinary protein loss, decreased glomerular filtration, and increased tubular reabsorption of sodium. The treatment may be summarized as follows: (1) bed rest; (2) low-sodium diet; (3) chlorothiazide, 500 to 1000 mg. twice daily (or hydrochlorothiazide in appropriate dosage); (4) if these procedures do not control edema in one week, a seven-day trial of hydrocortisone may be instituted; chlorothiazide is started on the last day of hydrocortisone therapy; (5) if there is no response to this therapy, administer 100 mg. of salt-poor human albumin intravenously every other day; this is an expensive procedure; (6) finally, parenteral mercurials may be tried if edema is severe and unresponsive to chlorothiazide.

Hepatic Disease. Since the edema associated with liver disease frequently originates

* Hydrochlorothiazide can be used interchangeably but in a dose ratio of 1:10, i.e., 1 mg. of hydrochlorothiazide is equivalent to 10 mg. of chlorothiazide.

from inadequate protein formation with reduction in blood protein osmotic pressure, the underlying liver disease should be attacked therapeutically. However, other factors such as decreased hepatic inactivation of salt-retaining steroids may be treated by agents acting to block the renal tubular reabsorption of sodium. An outline of treatment of the edema of hepatic disease follows: (1) low-sodium diet; (2) chlorothiazide, 1000 mg. twice a day (or hydrochlorothiazide in appropriate dosage); (3) in the presence of significant hypoalbuminemia (serum albumin less than 2 Gm./100 cc.), use salt-poor human albumin, 100 Gm. intravenously every other day, to achieve diuresis; the expense may be a contraindication here; (4) if inadequate response to intravenous albumin or chlorothiazide or hydrochlorothiazide is obtained, meralluride in a daily dosage of 2 cc. intramuscularly may be tried; (5) after massive edema is controlled, chlorothiazide or chlormerodrin may be used for maintenance.

Iatrogenic Steroid Edema. In the treatment of certain severe diseases, excessive dosages of ACTH, cortisone, or prednisone may be required. When sodium retention and edema become a problem, it is preferable to discontinue the steroid, but this is not always possible. The edema can usually be controlled by daily administration of chlorothiazide in a dosage of 500 to 1000 mg. every eight hours (or hydrochlorothiazide in appropriate dosage), or chlormerodrin in a dosage of 2 tablets four times a day. If these agents are not adequate when given alone, they should be used in combination.

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Pharmacology and Potency Estimation of Chlorothiazide and Thiazide Derivatives

Ralph V. Ford, M.D.

THE DEPARTMENTS OF PHARMACOLOGY AND MEDICINE,
BAYLOR UNIVERSITY COLLEGE OF MEDICINE, AND
THE VETERANS ADMINISTRATION HOSPITAL
HOUSTON, TEX.

INTRODUCTION

The use of benzothiadiazine compounds as diuretic agents has greatly facilitated the therapy of edematous states of varied etiology. An additional valuable use for these compounds has been in the therapy of hypertension, and the utility of the various compounds in this area appears to be proportional to their potency as diuretic agents.

It shall be our purpose to summarize pertinent clinical pharmacological information concerning four representative compounds: chlorothiazide, hydrochlorothiazide, flumethiazide, and dihydroflumethiazide. Their structural formulas are presented in figure 1.

POTENCY ESTIMATION

Using previously described techniques for the bioassay of diuretic agents,[1] which rely on the ability of the diuretic to enhance the urinary sodium excretion under controlled metabolic conditions, appropriate dosage response curves can be drawn for the various diuretics and calculations of potency estimations can be made.[1-4] The reference, or standard, diuretic is meralluride (administered intramuscularly) and its dosage response curve is termed "one." The appropriate positions of the four diuretic compounds under consideration are illustrated in figure 2. It is to be noted that the two-dose curve has been selected. Although the mg. dosage of drug varied among these compounds, the increase in sodium excretion falls within an observable range. Thus, such data relating to comparative potency estimations are clinically significant. That hydrochlorothiazide is 10 to 20 times more potent on a mg. basis than chlorothiazide may be of only academic interest. However, the fact that it is capable of producing a greater increase in sodium excretion may be of value to the patient with a more severe degree of edema.

ELECTROLYTE EXCRETION EFFECTS OF BENZOTHIADIAZINE DIURETICS

In view of the gross chemical similarity of these four thiazide derivatives, one would expect similar electrolyte excretion effects. The primary effect of these compounds is to augment the urinary excretion of sodium by the partial inhibition of the reabsorption of sodium in the renal tubule. This effect is paralleled by a change in chloride excretion. There is a mild inhibition of the tubular reabsorption of potassium and bicarbonate observed after the administration of all these compounds.

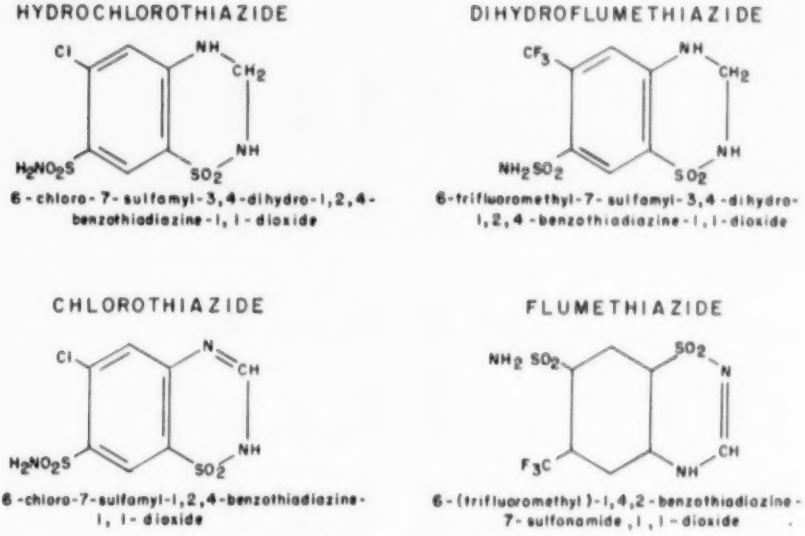

FIG. 1. Structural formulas of benzothiadiazine compounds.

These changes are accompanied by a slight increase in urinary *p*H during the height of diuretic activity. All these changes are accompanied and paralleled by an increase in urine volume.

There are certain minor differences in these four compounds (fig. 3). A critical examination of these data indicates that the hydro compounds produce a greater degree of sodium excretion without a proportional increase in potassium excretion. The sodium: potassium ratio will be increased with these compounds. This may

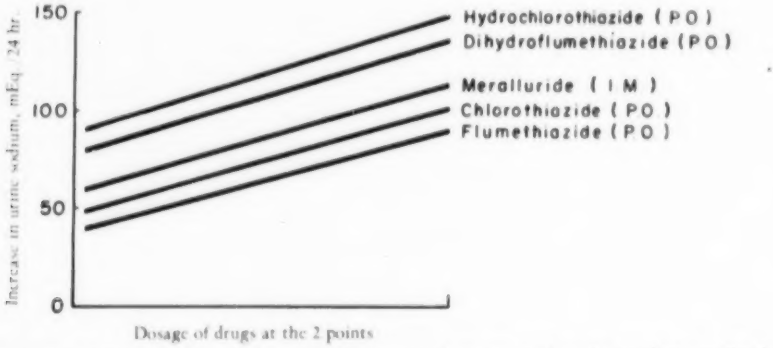

FIG. 2. Dosage response curves of various thiazide compounds as compared to the standard meralluride for the determination of potency. Dosage of drugs at the two points: Hydrochlorothiazide and dihydroflumethiazide, 25 and 50 mg.; chlorothiazide and flumethiazide, 1000 and 2000 mg.; meralluride, 1 ml. and 2 ml. (40 and 80 mm. of mercury).

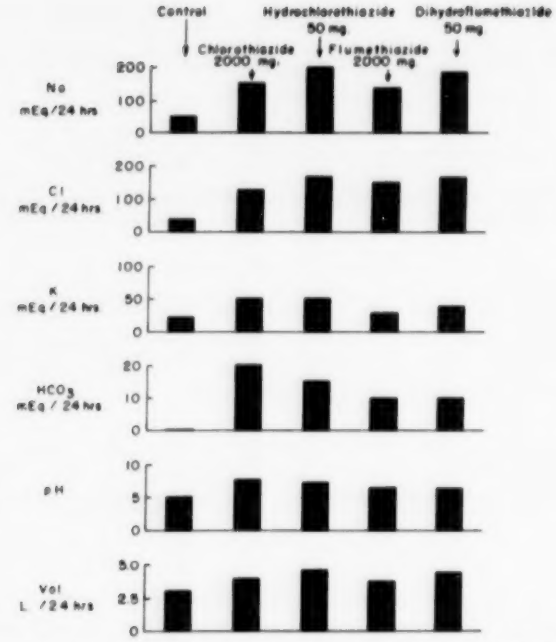

Fig. 3. Comparative urinary electrolyte excretion effects of various thiazide diuretics.

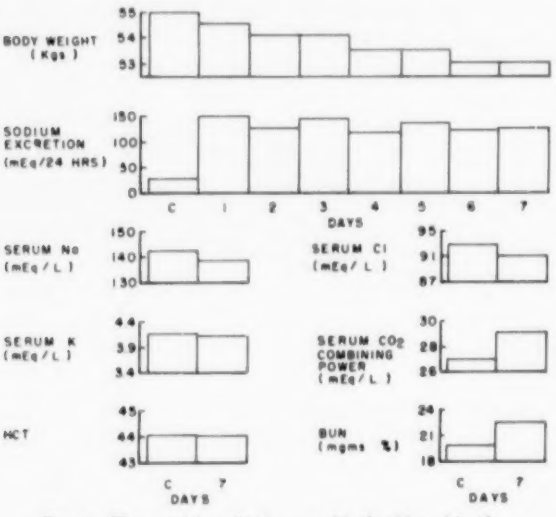

Fig. 4. The repetitive effectiveness of hydrochlorothiazide.

have clinical implications in that the tendency toward a clinical syndrome of hypokalemia would be less likely at comparable diuretic responses. It is to be noted further that this discrepancy in the sodium : potassium ratios is even more pronounced when the trifluoromethyl compounds are compared to the chlorothiazide compounds. Thus, there is a relatively greater excretion of sodium compared to potassium in these compounds than with chlorothiazide and hydrochlorothiazide. These changes are also associated with relatively less excretion of bicarbonate and less of an increase in *p*H with the trifluoromethyl compounds.

THE EFFECTS OF CONTINUOUS USE OF THE BENZOTHIADIAZINE DIURETICS

In contrast to other diuretic agents (carbonic anhydrase inhibitors and aminouracil compounds), these drugs are repetitively effective on continuous daily administration in their ability to augment the urinary excretion of sodium until excessive body stores of sodium have been depleted. Although there is a tendency toward the development of hypochloremic alkalosis, these changes do not become significant unless there is rigid salt restriction or the drug is continuously used after the therapeutic indication has subsided (fig. 4).

SUMMARY

The clinical pharmacology of benzothiadiazine derivatives as diuretic agents has been presented in terms of their relative potency and their relative effects on the urinary excretion of certain electrolytes; the clinical implications of these changes have also been noted.

BIBLIOGRAPHY

1. Ford, R. V., Moyer, J. H., and Spurr, C.: Clinical and laboratory observations on chlorothiazide (Diuril), A. M. A. Arch. Int. Med. *100*:582, 1957.
2. Ford, R. V.: The clinical pharmacology of hydrochlorothiazide, South. M. J. 52:40, 1959.
3. Montero, A. C.; Rochelle, J. B., and Ford, R. V.: The clinical pharmacology of flumethiazide, a diuretic agent, Am. Heart J. 57:484, 1959.
4. Ford, R. V., and Dennis, E. W.: The clinical pharmacologic investigation of dihydroflumethiazide. In press.

Report on Hospitalization Survey

A recent report by the U. S. National Health Survey estimates that approximately 16,738,000 people spent 143,322,000 days as patients in hospitals during the year ending June 30, 1958. About 70 per cent were hospitalized for a period of one to seven days, and another 18 per cent for 8 to 14 days. Roughly 60 per cent of hospitalizations involved surgery and obstetrics.

Pharmacology of the Thiazide Derivatives

Morton Fuchs, M.D., and Sanford Mallin, M.D.

CLINICAL PHARMACOLOGY SECTION, MEDICAL DEPARTMENT,
HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
PHILADELPHIA, PA.

INTRODUCTION

The introduction of chlorothiazide as a potent oral diuretic and antihypertensive agent has been a hallmark in therapeutic advancement and a stimulus for investigation of edema mechanisms and the pathophysiology of essential hypertension. Since the report of Novello and Sprague,[1] a number of derivatives of the benzothiadiazine group have been evaluated for clinical effectiveness and possible toxic effects.

Chlorothiazide has received wide acclaim as an efficient, nontoxic diuretic agent and its pharmacodynamics have been described in detail previously.[2] Chlorothiazide has its predominant action on sodium and chloride excretion and lesser effects on the potassium and bicarbonate ions. The oral administration of chlorothiazide results in diuretic activity within two hours, enduring for 6 to 12 hours, and the drug remains effective on continuous daily administration. The intravenously administered drug is rapidly excreted, and therefore, oral doses are more effective for total 24-hour natruresis. An oral dosage of slightly more than 1000 mg. is equivalent in potency to 1 ml. of meralluride administered intramuscularly. Significant natruretic activity appears with a dosage of 250 mg. and progresses up to a maximum effective dosage of 2000 mg. Dosages greater than 2000 mg. have no greater natruretic effect. Toxicity has presented only minor problems to date and usually has been manifested by minor gastrointestinal symptoms such as anorexia and nausea, frequently in the older age group. Occasional rashes of various forms have been seen as well as a rare case of thrombocytopenia, which improve after withdrawal of the drug.

The urinary electrolyte excretion pattern with chlorothiazide is shown in figure 1. Sodium excretion is effected maximally and the effect on chloride excretion is nearly equivalent to that on sodium. Potassium excretion varies up to 50 per cent of the total sodium excreted. The urinary electrolyte excretion pattern of the parenteral mercurial (meralluride) is also shown in figure 1. The patterns are quite similar but potassium excretion is less with meralluride.

Chlorothiazide has no significant influence on renal plasma flow or glomerular filtration rate with oral administration, and its diuretic effect is through blockade of reabsorptive (enzyme) mechanisms at the renal tubular level. A greater carbonic anhydrase-inhibiting effect is demonstrated at the higher dosage levels and increased potassium excretion is noted with larger dosages. Electrolyte imbalance, particularly sodium and potassium deficiencies, may occur with this agent as with any other potent diuretic, whether it be a benzothiadiazine derivative or a mercurial. These deficiencies do not appear to have produced a major clinical contraindication to the use of chlorothiazide if close patient observation is maintained.

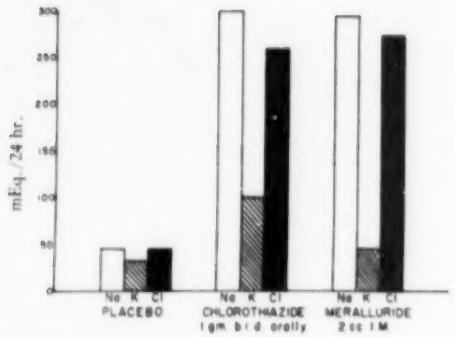

FIG. 1. Electrolyte excretion patterns of chlorothiazide and meralluride. The patterns are quite similar except that there is less potassium excretion with the mercurial.

Clinical experience indicates that a 500 mg. dose of chlorothiazide administered twice a day appears to be therapeutically adequate for controlling most cases of congestive heart failure. The degree of failure obviously will influence the maintenance dosage necessary to prevent accumulation of edema and the congestive failure symptoms. Chlorothiazide has also produced efficient results with edema associated with other pathological states such as hepatic disease, renal edema, and the edema of premenstrual tension and toxemia of pregnancy. The combined use of chlorothiazide and a mercurial diuretic may give additive effect in certain cases of edema that are less responsive to therapy.

OTHER BENZOTHIADIAZINE DERIVATIVES

The advancement that has been made in the therapy of edema with chlorothiazide has prompted active investigation of derivatives of the benzothiadiazine structure. Small changes in the basic structure of other groups of compounds have produced rather marked increase in potency and decrease in side effects.

A review of our experiences with three other benzothiadiazine derivatives is presented (fig. 2).

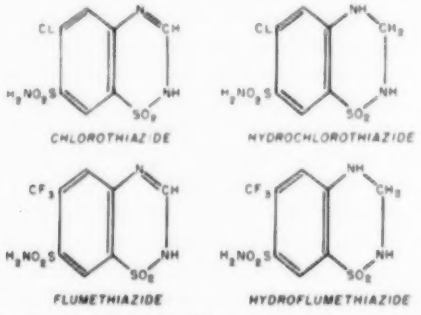

FIG. 2. Structural formulas of four benzothiadiazine derivatives.

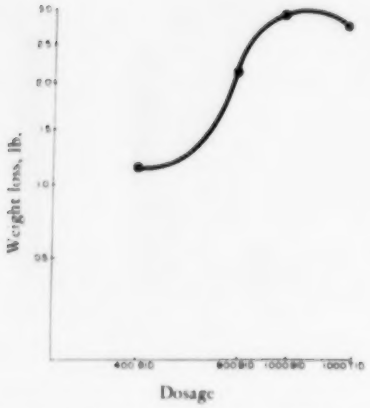

FIG. 3. Dose response curve as determined by weight loss in pounds in 48 hours in a group of cardiac patients given increasing dosages of trifluoromethylthiazide. The maximum effective dosage is 2000 mg. Dosages greater than 2000 mg. have no increased effectiveness. (Reprinted with permission from Fuchs et al.[3])

FLUMETHIAZIDE

Clinical Study. Trifluoromethylthiazide differs from chlorothiazide by replacing the chloride atom on the benzene ring by a trifluorinated methyl group (fig. 2).

This drug can be administered orally and intravenously with minimal side effects as with chlorothiazide.

A dose response curve was determined in the outpatient clinic by measuring the acute weight response in 48 hours in a group of cardiac patients to increasing dosages of the drug.[3, 4] The patients were free of diuretic therapy between each dose of the drug for at least five days and were on maintenance digitalis therapy. The dose response curve is presented in figure 3. The effective dosage range increases above a 200 mg. dosage to a maximum effective dosage of 2000 mg. Increasing dosages greater than 2000 mg. have no additional effectiveness. The maximum effective dosage of flumethiazide and chlorothiazide is the same, as determined by the acute weight loss experienced in 48 hours in the group of patients studied.

A chronic study in a group of 18 cardiac patients given 1000 mg. twice daily for five weeks resulted in an average weight loss of 1.2 lb. at the end of the study. These patients remained free of congestive failure symptoms and did not require additional mercurial diuretic therapy. There was no significant change in blood pressure in this group of patients but all but 1 were normotensive. Side effects were minimal and consisted of transient pruritus in 3 patients. It was not necessary to stop the drug at any time. Serum electrolyte concentrations, including sodium, potassium, chloride, blood urea nitrogen, carbon dioxide–combining capacity, and complete blood counts, were not significantly affected at the end of the five-week study.

Dose Response Curve and Electrolyte Studies. A sodium excretion dose response curve is shown in figure 4. This dose response curve is similar to the curve seen with

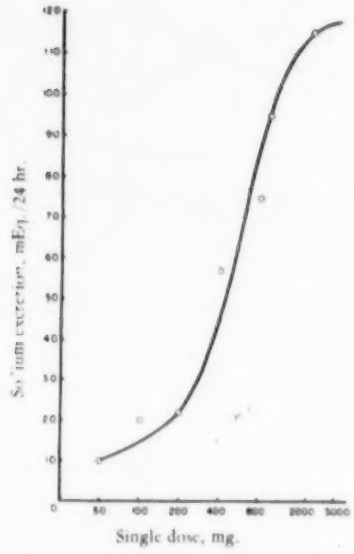

FIG. 4. Sodium dose response curve of flumethiazide. Onset of significant natruretic activity occurs at a dosage of approximately 200 mg. and progresses to a maximum effective dosage of 2000 mg. (Reprinted with permission from Fuchs et al.[6])

chlorothiazide.[2] Natruretic activity appears at the 200 mg. dosage and rapidly increases with larger dosages to the 2000 mg. level. Dosages greater than 2000 mg. do not have a greater saluretic effect. In figure 5, a dose response curve of the 24-hour urine potassium excretion is shown. Again, activity appeared to become prominent at the 200 mg. dosage level but further significant rise in potassium excretion was not found with dosages greater than 400 mg. With chlorothiazide,

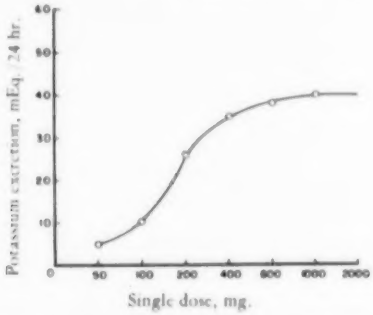

FIG. 5. Dose response curve of potassium excretion with increasing dosages of flumethiazide. There is significant activity at 200 mg. with little increase in potassium excretion at dosages above this level. (Reprinted with permission from Fuchs et al.[6])

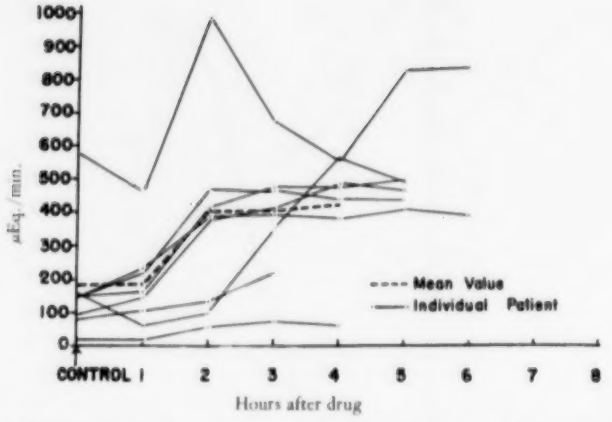

FIG. 6. Effects of oral flumethiazide on sodium excretion. The broken lines indicate observations on each individual patient and the heavy lines represent the mean average for all patients.

greater potassium excretion is stimulated at the high dosage levels, where carbonic anhydrase–inhibitory activity is greater.

Renal Studies. There was no change in renal plasma flow, glomerular filtration rate, or blood pressure in a group of patients given an 800 mg. dose of flumethiazide orally.[5, 6] An increase in sodium excretion is noted during the second hour after administration of flumethiazide and natruretic activity persists for more than six hours (fig. 6). Urine volume increases during the first hour of study and parallels the saluretic activity (fig. 7).

When flumethiazide is administered to nonedematous cardiac patients, there is an

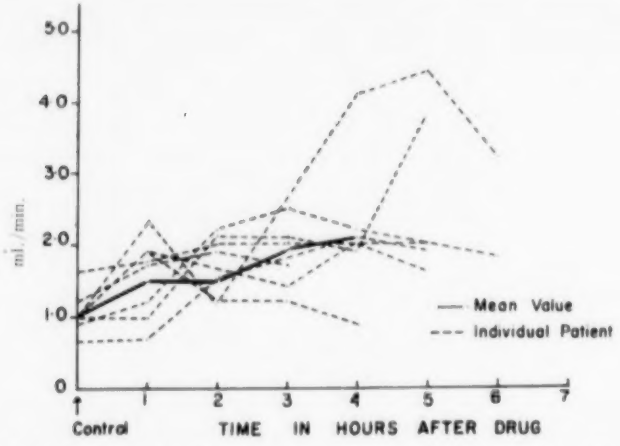

FIG. 7. Effects of oral flumethiazide on urine volume. See legend, figure 6.

increased sodium excretion lasting several days, which then falls to control excretion levels. Return of the 24-hour urine sodium excretion to control levels probably implies a state of relative sodium depletion and the clinical state of "dry weight" and cardiac compensation.

HYDROCHLOROTHIAZIDE

Clinical Study. Hydrochlorothiazide differs from chlorothiazide by the addition of two hydrogen atoms to the one unsaturated bond in the heterocyclic ring (fig. 2).

What would appear to be an apparently simple change in the basic chemical structure of chlorothiazide results in rather marked changes in the potency and qualitative aspects of electrolyte excretion patterns with hydrochlorothiazide. A dose response curve determined by acute weight loss in 48 hours on increasing dosages of hydrochlorothiazide in 20 cardiac patients is shown in figure 8. There is increasing effectiveness up to a maximum effective dosage of 200 mg. Dosages greater than 200 mg. had no increased effect on weight loss in this group of patients.[7–9]

The continuous administration of 200 mg. of chlorothiazide daily to 20 cardiac patients for five weeks produced no significant side effects, and no patient had symptoms of marked electrolyte imbalance. All patients remained free of congestive failure complaints and did not require additional mercurial diuretic therapy. These patients had required a mercurial injection weekly prior to the study. Serum electrolyte concentrations at the end of the chronic five-week study showed an average drop of 5 mEq./liter for sodium and potassium. The blood urea nitrogen rose an average of 5 mg./100 ml. In 9 patients there was a rise in blood urea of 5 mg./100 ml. or more. The blood urea rose in 16 of 20 patients studied and was at a lower concentration in 4 of the patients at the end of the five-week study period. There appeared to be no significant influence on the serum potassium or carbon dioxide concentrations, and blood counts remained unchanged.

Dose Response Curve and Electrolyte Studies. Electrolyte response curves for sodium, potassium, and chloride to increasing dosages of hydrochlorothiazide are shown in figure 9. A significant increase in electrolyte excretion starts at the 25 mg. dose level and increases to a maximum at the 200 mg. dose level. This would appear to be the maximum effective dosage for sodium excretion, and no further significant increase

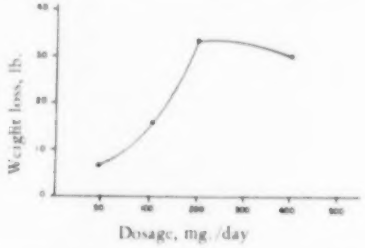

FIG. 8. Weight loss in 48 hours with increasing dosages of hydrochlorothiazide in 20 cardiac patients. A maximum weight loss was obtained with 100 mg. twice daily and no greater weight loss was obtained with larger dosages. (Reprinted with permission from Fuchs et al.[8])

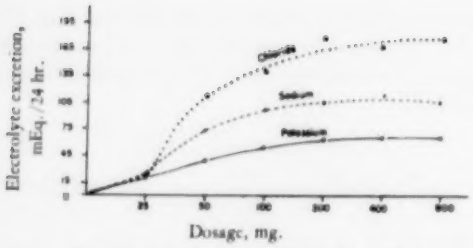

FIG. 9. Dose response curves for sodium, potassium, and chloride with increasing dosages of hydrochlorothiazide. (Reprinted with permission from Fuchs et al.[9])

in excretion is produced with a dosage larger than 200 mg. There is a 10 to 1 ratio in the dosage range between chlorothiazide and hydrochlorothiazide. The chloruretic response is noticeably larger than the natruretic response, and the potassium excretion is approximately one half that of the sodium (fig. 10). Potassium response increases progressively up to the maximum effective dosage as opposed to a stable response at the higher dosage levels with flumethiazide.

When a single dose of hydrochlorothiazide is given, there is a noticeable increase in sodium and potassium excretion apparent in two hours, with a duration of activity for 12 hours or more and then a return to control levels. Doses administered twice daily result in a significant increase in sodium and potassium excretions after each dose and give a larger sodium excretion in 24 hours than a single dose of equivalent amount (figs. 11 and 12). Urine volume follows the increase in sodium excretion. Figure 13 shows the sodium excretion after the daily administration of 50 mg. of hydrochlorothiazide three times a day in a patient with congestive heart failure with edema. Sodium excretion was initially much greater than control levels and then gradually declined to control levels, at which time the weight was stable and all clinical evidence of edema had been lost. On the first, ninth, and fourteenth days of therapy, 2 ml. of mercaptomerin was given, which produced an additive natruretic effect. While the patient retains excess sodium stores and edema,

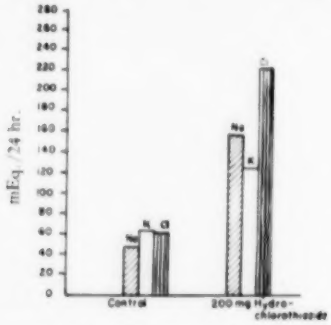

FIG. 10. Electrolyte excretion pattern of hydrochlorothiazide. Chloride excretion is greater than that of sodium, and potassium excretion is approximately one half the sodium excretion. (Reprinted with permission from Fuchs et al.[9])

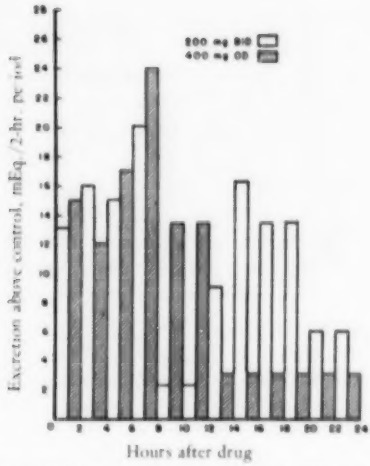

FIG. 11. Electrolyte excretion of sodium, measured at two-hour intervals after a single 400 mg. dose of hydrochlorothiazide once daily and a 200 mg. dose given twice daily (12 hours apart). (Reprinted with permission from Fuchs et al.[9])

the sodium excretion remains above control levels with the use of the thiazide diuretics until the excess sodium stores are depleted and cardiac compensation and the edema free state are attained.

Renal Studies. The effects of an intravenous dose of hydrochlorothiazide (200 mg.) on renal hemodynamics are shown in figure 14. Immediately after intravenous administration of the drug, there was a temporary reduction in glomerular filtration rate, which returned to control values within one hour. Despite the temporary decrease in glomerular filtration rate, there was an increase in sodium, chloride, and water excretion by the first hour after administration of the hydrochlorothiazide. Renal plasma flow increased slightly. Orally administered hydrochlorothiazide had no influence on glomerular filtration rate or renal plasma flow. It can be concluded

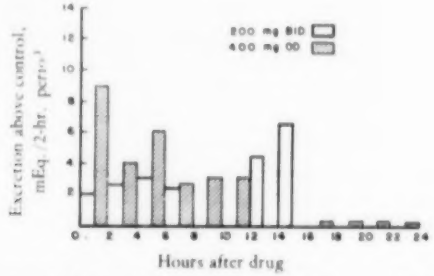

FIG. 12. Electrolyte excretion of potassium measured at two-hour intervals after a single 400 mg. dose of hydrochlorothiazide once daily and a 200 mg. dose given twice daily (12 hours apart). (Reprinted with permission from Fuchs et al.[9])

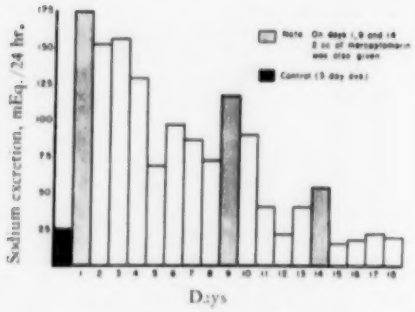

FIG. 13. The sodium excretion of an edematous cardiac patient receiving 50 mg. of hydrochlorothiazide three times a day for 18 days. During this period the patient lost all clinical evidence of edema fluid. A marked increase in sodium excretion is seen with the hydrochlorothiazide, and this is augmented by mercaptomerin administered on the first, ninth, and fourteenth days. (Reprinted with permission from Fuchs et al.[9])

that the natruretic and diuretic activity of the drug is a tubular response and not due to any noticeable change in renal hemodynamics.

After the oral administration of hydrochlorothiazide, the drug appears in the urine within one hour and reaches a maximum excretion within three hours. Less than 25 per cent of the entire amount of the ingested drug is excreted within five hours.

HYDROFLUMETHIAZIDE

Hydroflumethiazide differs from chlorothiazide by replacing the chloride atom

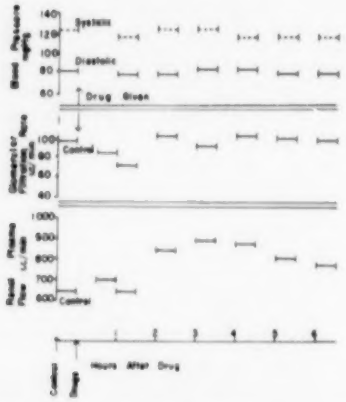

FIG. 14. The response of renal hemodynamics to a 200 mg. intravenous dose of hydrochlorothiazide is shown. There is no significant effect on either the systolic or diastolic pressure. There is a slight transient decrease in glomerular filtration and an increase in renal plasma flow but neither vary to any significant degree. (Reprinted with permission from Moyer et al.[7])

with a trifluoromethyl group and saturation of the heterocyclic ring with two hydrogen atoms (fig. 2).

Clinical Study. A dose response curve as determined by acute 48-hour weight loss in a group of cardiac patients shows significant activity at the 50 mg. dosage level and the maximum effective dosage is 400 mg. Dosages larger than 400 mg. do not produce a greater weight loss.

Continuous administration of 200 mg. of hydroflumethiazide daily for six weeks to 24 cardiac patients did not produce any apparent toxic side effects and all patients except 1 maintained good cardiac compensation. Parenteral mercurials had to be administered to 1 patient who was in a state of refractory edema, which was not responsive to the maximum effective dosages of the other thiazide derivatives. There was no clinical evidence of electrolyte imbalance, and serum electrolyte studies and complete blood counts at the end of the study did not show any significant changes.

Dose Response Curve and Electrolyte Studies. The electrolyte response curves to increasing dosages of hydroflumethiazide are similar to those with hydrochlorothiazide in that there is marked activity demonstrated in the dosage range of 25 to 400 mg. and chloride excretion significantly exceeds sodium excretion. The maximum dosage for sodium excretion is in the 200 to 400 mg. range. Potassium excretion is increased, but there is a similarity to the flumethiazide excretion curve in that maximum potassium excretion is reached in the lower dosage range and does not significantly increase with the higher dosages. This is not apparent with chlorothiazide and hydrochlorothiazide.

Renal Studies. The oral administration of 200 mg. of hydroflumethiazide has no effect on the glomerular filtration rate, renal plasma flow, or blood pressure, but there is a significant increase in the natruretic activity by the second hour after administration. Urine volume increases and parallels the increase in sodium excretion. Increased natruretic activity remains apparent for more than six hours. The activity of this drug also depends on its inhibition of reabsorptive mechanisms at the renal tubular level.

DISCUSSION

The four benzothiadiazine derivatives that have been described are all potent nontoxic diuretic agents. However, when we review their individual characteristics it becomes apparent that two basic types emerge. One type includes the nonhydrogenated and the other the hydrogenated derivatives. Chlorothiazide and flumethiazide both have a similar sodium dose response curve with the onset of significant natruretic activity above a 200 mg. dosage to a maximum effective dosage of 2000 mg. Both drugs have an effective clinical dosage range of the same magnitude. It is also apparent that the electrolyte excretion patterns of chlorothiazide and flumethiazide are similar in regard to sodium and chloride excretion. However, 24-hour potassium excretion of the chlorinated derivative appears to be greater than with the trifluorinated form. In addition, potassium excretion increases with increasing dosages of chlorothiazide up to a maximum dosage, whereas with flumethiazide, maximum potassium excretion appears at a lower dosage level and does not increase significantly above this dosage.

TABLE I

Weight Loss in Pounds Produced in 48 Hours by the Maximum Effective Dosage of Four Thiazide Derivatives

	Maximum effective dosage of drug			
	Chlorothiazide, 2000 mg.	Flumethiazide, 2000 mg.	Hydrochlorothiazide, 200 mg.	Hydroflumethiazide, 400 mg.
Weight loss, lb.	2 9	2 9	3 3	3 43
p value <	0 001	0 001	0 001	0 001

When chlorothiazide and flumethiazide are hydrogenated, a new set of characteristics is created, which produces the second basic type of benzothiadiazine derivative. By the simple addition of two hydrogen atoms to the heterocyclic ring (fig. 2), the effective dosage range of both the chlorinated and the trifluoromethyl forms is reduced to approximately one tenth or less. With the hydrogenated group, the sodium dose response curve ranges from 25 mg. or less to a maximum effective dosage of 200 to 400 mg. (fig. 15). However, the maximum effective dosages of the hydrogenated and the nonhydrogenated groups produce equivalent sodium excretion. Another rather definite change as a result of hydrogenation is the change in electrolyte excretion pattern. By the addition of the hydrogen atoms, the compounds become much more potent chloruretic agents, with results significantly above sodium excretion levels. This occurs with both the chloride and trifluoromethyl derivatives. Potassium excretion presents the same characteristics in this group as it does in the nonhydrogenated group.

When weight response and clinical impressions are used as criteria of diuretic effectiveness, it appears that there is a somewhat greater effect with the hydrogenated forms. However, total sodium excretion is quite similar in both groups. Possibly the increased potency of the hydrogenated drugs may be better measured by their increased chloruretic effect rather than by the natruretic effect.

All four drugs have the same clinical application and all are capable theoretically

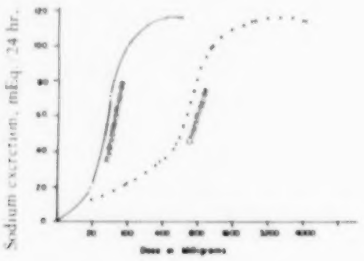

FIG. 15. Sodium dose response curve of hydrochlorothiazide (and hydroflumethiazide) and chlorothiazide (and flumethiazide). It is apparent that the nonhydrogenated forms have a dosage range approximately 10 times that of the hydrogenated group. (Reprinted with permission from Fuchs et al.[5])

of producing electrolyte depletion syndromes. Adequate patient observation is mandatory in order to determine the early clinical signs of sodium and potassium deficiencies. The elevation of the blood urea nitrogen that may be seen with continuous administration of these drugs may be a result of decreased glomerular filtration, secondary to progressive dehydration and hyponatremia. This would be accentuated in the presence of renal impairment existing before the use of the drug. A further possibility may be an increase in protein catabolism with the benzothiadiazine agents.[10]

Toxic effects have presented no major difficulties with any of the drugs studied to date. Only prolonged observation over a period of several years will give the final conclusive assurance that these agents are truly nontoxic.

At the present time we are actively engaged in studying other derivatives of the benzothiadiazine group. It will be interesting to compare both the pharmacological characteristics and clinical effectiveness of these agents with those of drugs that are being used in practice today.

SUMMARY

1. A summary of the pharmacology of four derivatives of the benzothiadiazine group of diuretics is presented.

2. These drugs are considered a marked advancement in the field of diuretic therapy and may be only the initial steps in the development of even more effective and safe agents for the therapy of edema and hypertension.

BIBLIOGRAPHY

1. Novello, F. C., and Sprague, J. G.: Benzothiadiazine dioxides as novel diuretics, J. Am. Chem. Soc. 79:2028, 1957.
2. Ford, R. V., Moyer, J. H., and Spurr, C. L.: Clinical and laboratory observation on chlorothiazide (Diuril), A. M. A. Arch. Int. Med. *100*:582, 1957.
3. Fuchs, M., Bodi, T., and Moyer, J. H.: Evaluation of flumethiazide (trifluoromethylthiazide) in the out-patient clinic, Am. J. Cardiol. 3:676-680, May, 1959.
4. Fuchs, M., Mallin, S. R., Irie, S., and Lippman, E.: The diuretic effects of flumethiazide (Ademol), a new benzothiadiazine derivative, Postgrad. Med. In press.
5. Bodi, T., Fuchs, M., Irie, S., and Moyer, J. H.: Further observations on flumethiazide—a new oral diuretic, Am. J. Cardiol. In press.
6. Fuchs, M., Bodi, T., Mallin, S., and Moyer, J. H.: The diuretic activity of flumethiazide (Ademol), Monographs of Therapy, Squibb Institute *4*:43-50, April, 1959.
7. Moyer, J. H., Fuchs, M., Irie, S., and Bodi, T.: Some observations on the pharmacology of hydrochlorothiazide (Hydrodiuril), Am. J. Cardiol. 3:113, 1959.
8. Fuchs, M., Bodi, T., Irie, S., and Moyer, J. H.: Preliminary evaluation of hydrochlorothiazide (Hydrodiuril), M. Rec. & Ann. *51*:872, 1958.
9. Fuchs, M., Mallin, S., Irie, S., Hernando, L., and Moyer, J. H.: A review of the pharmacology and clinical observations of hydrochlorothiazide, A. M. A. Arch. Int. Med. To be published.
10. Corcoran, A. C.: Hahnemann Hypertension Symposium, Philadelphia, W. B. Saunders Co., 1958.

The Use of Chlorothiazide and Hydrochlorothiazide in the Treatment of Congestive Heart Failure

Albert N. Brest, M.D.

HAHNEMANN MEDICAL COLLEGE AND HOSPITAL; BAILEY THORACIC CLINIC
PHILADELPHIA, PA.

Chlorothiazide has been available for clinical use for a period of two years. During this relatively brief interval, it has become recognized as the most effective oral diuretic available for the treatment of the various edema states. The almost immediate clinical popularity of this drug attests to its usefulness and pharmacological superiority over all previous oral diuretics.

More recently another member of the benzothiadiazine family, hydrochlorothiazide, has been introduced. The clinical recognition of the diuretic effectiveness of this drug has been similar to that of chlorothiazide. Although long-term studies are not yet available, early reports suggest that hydrochlorothiazide may be even more effective than chlorothiazide.

It is the purpose of this report to review the experiences that have been recorded with these two drugs and to compare their usefulness in the treatment of congestive heart failure.

EXPERIENCES WITH CHLOROTHIAZIDE

The effectiveness of chlorothiazide as a diuretic is dependent on its ability to inhibit the renal tubular reabsorption of sodium and chloride (and, secondarily, water). Although this drug appears to have some carbonic anhydrase inhibitory action, its primary pharmacodynamic effect more closely resembles that of the potent organomercurial compounds. However, the specific mode of action of chlorothiazide still remains undetermined.

Since the mercurials have long been recognized as the most effective available diuretics, it is important to compare the potency of each new diuretic with that of the mercurials. By means of standard bioassay techniques, Ford[1] has shown that chlorothiazide (2000 mg.) is 80 per cent as potent orally as parenteral meralluride (2 ml.). Bayliss et al[2] have similarly reported that the comparative potencies of mersalyl and chlorothiazide are equal.

In addition, it has been found that chlorothiazide may be effective at times when the mercurials fail to produce any significant diuresis. Bayliss et al[2] discussed 11 patients who had shown little or no response to biweekly injections of mersalyl. The refractoriness in these patients could not be attributed to any electrolyte imbalance. Chlorothiazide produced significant or complete clearing of edema in 9 of the 11 patients. Laragues[3] has reported similar findings.

Finally, it has been demonstrated that chlorothiazide may increase the response

to mercurials when both diuretics are given together.[3] This finding has obvious clinical connotations.

Thus, chlorothiazide exhibits many of the features of the ideal diuretic: (1) it is effective when administered orally, (2) it is as potent as a mercurial diuretic given parenterally, (3) it may be effective when mercurials fail, and (4) when given in combination, chlorothiazide and mercurials may have an additive effect.

Multiple clinical reports attest to the efficacy of chlorothiazide. Fishman et al[4] found that 71 of 87 patients treated with chlorothiazide had a significant to marked reduction in peripheral edema. Dinon et al[5] reported similar effectiveness in a larger series of 121 patients, and many other like reports are now available.

Various types of electrolyte imbalance may occur with the administration of chlorothiazide. Hypochloremic alkalosis and hyponatremia are particularly likely when vigorous chlorothiazide therapy is combined with rigid salt restriction. However, these complications can be readily corrected by the use of ammonium chloride in the former instance or hypertonic saline solution in the latter.

Another electrolyte complication is potassium deficiency. Hypokalemia either may occur during the course of extreme diuresis or else may appear unexpectedly in certain persons in the absence of a significant diuresis, thus emphasizing the marked kaluretic property of chlorothiazide. However, from a practical standpoint, this latter complication is uncommon in the patient receiving less than 1 Gm./day and can readily be prevented by the prophylactic administration of potassium salts or citrus fruits in the patient receiving more than 1 Gm. daily.

Chlorothiazide appears to be remarkably free of toxic effects. However, Dinon et al[5] reported neutropenia and thrombocytopenia as a possible, although unconfirmed, toxic complication in 1 instance. The incidence of side effects is likewise small; they consist primarily of gastrointestinal complaints and minor skin eruptions.

According to Moyer,[6] the patient with considerable heart failure in whom immediate diuresis is needed is best treated initially with a dosage of 1000 mg. every 8 to 12 hours. Unless the diuretic response is excessive, the dosage can be maintained at this level until the patient approaches dry weight, at which time the dosage can be reduced gradually until the minimum effective dosage has been determined. The usual maintenance dosage will be 250 to 500 mg. daily, although larger dosages may be required in individual instances.

When chlorothiazide is used for patients who are not in intractable heart failure, the dietary salt intake can be liberalized. This precaution will also lessen the likelihood of electrolyte imbalance. Likewise it is not necessary to discontinue the drug intermittently, for tolerance to chlorothiazide has been shown not to occur.

EXPERIENCES WITH HYDROCHLOROTHIAZIDE

Clinical pharmacological studies have demonstrated that hydrochlorothiazide is also a potent diuretic that resembles chlorothiazide qualitatively but is at least 10 times more active.[7, 8] Both drugs have marked saluretic properties; however the urinary loss of potassium is relatively less after the administration of this drug than with chlorothiazide. This latter effect implies a clinical advantage for hydro-

chlorothiazide, for one might expect that the complication of hypokalemia will be less with the newer analogue.

Ford[7] has demonstrated that in comparison with the mercurial diuretics, hydrochlorothiazide is 1.4 times as potent after oral administration as meralluride after parenteral administration. In this respect, hydrochlorothiazide appears to be even more effective than chlorothiazide.

Although long-term studies are not yet available, several clinical reports of the diuretic effectiveness of hydrochlorothiazide are now available. Brest and Likoff[9] reported complete control of heart failure in 16 of 20 patients treated with this drug. Perhaps more significant is the fact that 9 of 12 patients who had been refractory to previous diuretic therapy for congestive failure were successfully controlled with hydrochlorothiazide. Similarly significant is the fact that 6 of the 9 had previously been treated with chlorothiazide.[10]

Hypochloremic alkalosis and hyponatremia may occur with the administration of hydrochlorothiazide but can be readily controlled, as just outlined. Hypokalemia is less likely than with chlorothiazide, and a low incidence of side effects has been reported thus far, similar to the frequency with chlorothiazide.

Moyer et al[5] reported that the maximum effective dosage of hydrochlorothiazide appears to be 100 mg. twice daily and the minimum effective dosage needed to produce natruresis is 20 to 25 mg. The larger dosage should be administered until the patient approaches dry weight, at which time there can be a gradual reduction to the effective minimum dosage.

Ford[7] reported the absence of the development of tolerance to this drug after consecutive daily administration. This suggests that the drug can be used daily in the treatment of heart failure with repetitive effectiveness.

CONCLUSIONS

Digitalis, rest, and reduction in salt intake constitute the basic therapeutic regimen for congestive heart failure. However, the use of diuretic therapy plays a major supporting role, either by facilitating a more rapid response or else by controlling an otherwise intractable congestive state. Hence, the constant search for effective diuretic agents is of great clinical importance.

Sufficient evidence is now at hand to indicate that chlorothiazide is the most effective proved oral diuretic presently available. Its diuretic potency is similar to that of the mercurials, and in fact, it may be effective when the latter are not. Also, it has been shown that chlorothiazide may increase the response to mercurials when both agents are given together. These factors substantiate the value of this potent diuretic agent.

Although various types of electrolyte imbalance may occur with the use of chlorothiazide, these complications can be readily controlled by appropriate replacement therapy and may possibly be prevented by proper prophylaxis. Chlorothiazide appears to be remarkably free of toxic reactions and there is a low incidence of side effects.

More recently, hydrochlorothiazide has become available for clinical use. Certain

pharmacological features suggest that this new drug may ultimately prove to be even more effective than chlorothiazide. The comparative potency of hydrochlorothiazide with the mercurials is even greater than that attained with its precursor, and the newer drug may be effective when chlorothiazide is not. Finally, the lesser kaluretic effect with hydrochlorothiazide indicates another advantage for the newer analogue.

In summary, the use of chlorothiazide and hydrochlorothiazide represents a significant advance in the therapeutic armamentarium for congestive heart failure.

BIBLIOGRAPHY

1. Ford, R. V.: Diuretic therapy of congestive heart failure, Ann. New York Acad. Sc. *71*:397, 1958.
2. Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Zilva, J. F.: The use of chlorothiazide in the treatment of edema: A comparison with other diuretic agents, Ann. New York Acad. Sc. *71*:442, 1958.
3. Laragh, J. H.: Some effects of chlorothiazide on electrolyte metabolism and its use in edematous states, Ann. New York Acad. Sc. *71*:409, 1958.
4. Fishman, S. I., Jaffe, R. J., Schwartz, G., Stechel, G. H., Franhauser, A., Behr, D. J., and Yarvis, J. J.: Chlorothiazide: A new approach to the therapy of edematous states, New York J. Med. *59*:1679, 1958.
5. Dixon, L. R., Kim, Y. S., and VanderVeer, J. B.: Clinical experience with chlorothiazide (Diuril), with particular emphasis on untoward responses, Am. J. M. Sc. *236*:533, 1958.
6. Moyer, J. H.: The use of diuretics in clinical medicine, Geriatrics *13*:489, 1958.
7. Ford, R. V.: The clinical pharmacology of hydrochlorothiazide, South M. J. *52*:40, 1959.
8. Moyer, J. H., Fuchs, M., Irik, S., and Bodi, T.: Some observations on the pharmacology of hydrochlorothiazide, Am. J. Cardiol. *3*:113, 1959.
9. Brest, A. N., and Likoff, W.: Hydrochlorothiazide in the treatment of congestive heart failure, Am. J. Cardiol. *3*:144, 1959.
10. Brest, A. N., and Likoff, W.: Unpublished data.

Urology Award

The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been graduated not more than 10 years and to hospital interns and residents doing research work in urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Palmer House, Chicago, May 16-19, 1960.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland. Essays must be in his hands before Dec. 1, 1959.

Chlorothiazide and Hydrochlorothiazide in the Treatment of Congestive Heart Failure

John W. Keyes, M.D., Gerald M. Breneman, M.D., and Hernan Alvarez, Jr., M.D.

ADULT CARDIOLOGY DIVISION, DEPARTMENT OF MEDICINE, HENRY FORD HOSPITAL
DETROIT, MICH.

INTRODUCTION

In the past two years, a new class of potent oral diuretic agents, derived from the aromatic sulfonamides and belonging to a group known as benzothiadiazines, has been introduced to the medical profession. The first major breakthrough in producing a nontoxic and highly active oral diuretic resulted in the development of chlorothiazide, 6-chloro, 7-sulfamyl, 1, 2, 4-benzothiadiazine-1, 1-dioxide.[1] Since then, a second and more powerful derivative, hydrochlorothiazide, has been synthesized; it is designated as 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide. Both of these compounds are very active saluretic agents, causing the excretion of large amounts of sodium, chloride, and, to a lesser extent, potassium. It is to this activity that the drugs owe their effectiveness in the management of edema states, particularly congestive heart failure. Hydrochlorothiazide differs from chlorothiazide in having no double bond in the heterocyclic ring and appears to be several times more effective in its diuretic activity mg. for mg., as will be shown later.

CHLOROTHIAZIDE

Mode of Administration. The plan was to give 500 mg. two or three times daily at six-hour intervals for two, three, or four days consecutively with a rest period of three or four days between, if prolonged use was planned. However, maximal response was obtained with 250 mg. doses administered in the same manner. The dosage must be determined for each patient; some patients may have congestive failure of such severity as to need continuous daily use, in order to keep them free of edema or fluid accumulation. It is surprising to see the variations in dosage requirement for different patients. Once stable weights can be attained with maximal improvement on a particular dosage, this should be approximately what the individual patient will require for maintenance. It should be noted that giving larger dosages (in excess of 2000 mg. in 24 hours) may not increase diuretic effectiveness and may only lead to possible greater loss of potassium.

Method of Study. Fifty patients who were in congestive heart failure received chlorothiazide as the principal diuretic, and in some cases, ammonium chloride was utilized in conjunction with chlorothiazide. A uniform 400 mg. sodium diet was used; all but 2 patients were on adequate digitalis maintenance. The follow-up period ranged from one week to seven months, and the degree and duration of failure made it possible to place each patient in one of four groups.

Group 1. Five patients who had not received diuretics constituted this group.

Chlorothiazide was administered instead of mercurials, in a dosage of 250 mg. three times a day for three consecutive days of each week. Etiology of the failure in this group was arteriosclerotic heart disease in 3 patients, hypertensive heart disease in 1, and rheumatic heart disease in 1. The average weight loss for each initial three-day period was 6 lb.

GROUP 2. This group consisted of 25 patients in chronic congestive failure whose past treatment was either an occasional mercurial injection, an oral mercurial, or a nonmercurial diuretic. This group of patients included 9 with arteriosclerotic heart disease, 3 with hypertensive cardiovascular disease, and 13 with rheumatic heart disease. All patients were followed from six weeks to four months.

Chlorothiazide was again administered in periods of three consecutive days each week, in doses of 250 to 500 mg. three times each day. One patient in this group, however, was under good control with only 125 to 250 mg. once a week. Weight loss for the group ranged between 3 and 8 lb., with an average loss of 5 lb. during each three-day period. Diuresis in all cases was felt to be at least equal to that achieved with previous medications. One patient, when changed from an oral mercurial to chlorothiazide, lost an additional 5 lb. in the first four days of treatment.

GROUP 3. This group included 17 patients in chronic congestive failure, who had required mercaptomerin or chlormerodrin by injection once or twice weekly or once every two weeks. There were 11 cases of arteriosclerotic heart disease, 1 case of hypertensive cardiovascular disease, and 5 cases of rheumatic heart disease. Chlorothiazide therapy was substituted in doses of 250 to 500 mg. three times daily for three consecutive days of each week. Initial weight loss with chlorothiazide averaged 6 lb., with 1 patient losing 12 lb. No patient failed to respond and achieve a controlled state.

GROUP 4. There were 3 patients with arteriosclerotic heart disease in intractable congestive failure, refractory to mercurial diuretics. Chlorothiazide also failed to induce diuresis.

The results of chlorothiazide therapy for congestive failure in these four groups are indicative of its effectiveness in all usual forms of heart disease. A more uniform and sustained diuresis, producing an edema-free state, is also noted with chlorothiazide. There is not as much reaccumulation of fluid between periods of drug administration as is the case with intermittent mercurials.

The drug was exceedingly well tolerated by all patients in this series and no gastrointestinal side effects were noted. There was 1 instance of a mild erythematous papular rash of the trunk and extremities, which cleared promptly on withdrawal of the drug. All patients showed a mild hypochloremia, but there was no case of serious electrolyte depletion. No hematological or neurological disorders were noted.

Discussion. An average initial dosage of 500 mg. two to three times a day over a 15-hour period was found to be most effective; an occasional patient required twice this dosage, but many responded adequately to half this amount of drug. The smallest effective dosage should be sought through individualization of each case. This can be quickly determined. Moderate congestive failure usually responds with three or four consecutive days of drug administration per week. Patients in severe failure may do well with daily administration.

TABLE I

Type of Congestive Failure of 32 Patients Treated with Hydrochlorothiazide

Etiology	Grade I	Grade II	Grade III	Total
Arteriosclerotic	4 (1)*	7 (2)*	3	14
Rheumatic	3	10	1 (1)*	14
Hypertensive	1	1	0	2
Congenital	0	1	0	1
Cor pulmonale	0	1	0	1
Total	8	20	4	32

* Figures in parentheses indicate number with toxic changes.

Dosages exceeding 2000 mg./day of chlorothiazide produce an excessive urinary bicarbonate loss, because of inhibition of carbonic anhydrase by the drug. This mechanism is not evident with the usual dosages.

Salt restriction may be eliminated in some patients while on chlorothiazide, a factor that greatly enhances the patient's sense of well-being.

HYDROCHLOROTHIAZIDE

Mode of Administration. The exact dose of hydrochlorothiazide comparable to 500 mg. of chlorothiazide has not been agreed on but would appear to be somewhere between 50 and 100 mg. Our plan was to match 50 mg. of hydrochlorothiazide to 500 mg. of chlorothiazide. Some patients seemed to do as well on this program, but others required 150 mg. of hydrochlorothiazide each day to equal 1000 mg. of chlorothiazide. It would appear that if the effects of hydrochlorothiazide are more prolonged,[2] a wider spacing of eight hours between doses might provide longer coverage and better diuretic effects. The drug also may be continued for long periods of extended therapy, the same as chlorothiazide, but a word of caution should be given to watch closely for electrolyte depletion effects, as hydrochlorothiazide does appear to depress chlorides more than chlorothiazide does.

Hydrochlorothiazide may be administered intravenously in its lyohydrochlorothiazide form—50 mg. diluted in 5 to 10 ml. of distilled water. This amount comes very close to equaling 2 ml. of mercaptomerin or meralluride in effectiveness.

Method of Study. Thirty-two patients with congestive heart failure were treated with hydrochlorothiazide. Fourteen patients had arteriosclerotic heart disease, 14 had rheumatic heart disease, 2 had hypertensive heart disease, and there was 1 case each of congenital heart disease (probable atrial septal defect) and cor pulmonale.

The subjects were divided into three grades of congestive failure, as follows (table I): Grade I: patients with mild to moderate degrees of congestive heart failure, manifested usually by dyspnea, moist basilar râles, hepatic congestion, and slight edema; grade II: patients with severe congestive failure, usually with marked edema and/or ascites; grade III: patients with severe congestive failure who had become resistant or refractory to previously used diuretic agents.

All patients received digitalis, and the majority had had prior diuretic therapy,

mercurials, and/or chlorothiazide. One patient in grade I failure and 1 in grade II had received no previous diuretic. Grade I patients were maintained on 400 to 1600 mg. sodium diets as indicated, while those in grades II and III were maintained on the 400 mg. sodium diet.

Twenty-four patients were hospitalized, and the remaining 8 were followed at one- to four-week intervals in the outpatient department. Daily weight was obtained. Blood counts, urinalyses, blood urea nitrogen and serum electrolyte determinations were obtained once or twice weekly for all hospitalized patients. Clinic patients were checked with less regularity, though several maintained a daily weight chart at home.

Results. GRADE I. Eight patients were classified as having grade I congestive failure: 4 with arteriosclerotic heart disease, 3 with rheumatic heart disease, and 1 with hypertensive heart disease. Seven of the patients had been treated with previous diuretic regimens, all with good response. When changed to hydrochlorothiazide, 6 of the 7 responded as well to this agent. One patient (case 1) demonstrated a superior response to a mercurial diuretic.

Case 1. N. A., a 71-year-old white woman who had been followed in the outpatient department since March, 1957, had a diagnosis of rheumatic heart disease, aortic insufficiency, and cardiac decompensation. She was maintained on a 1 Gm. salt diet, gitalin, 0.5 mg. daily, and intermittent injections of mercurial diuretics.

She was admitted to the hospital on Dec. 14, 1958, because of increasing dyspnea, palpitation, and ankle edema of two weeks' duration. Weight on admission was 106 lb.; after four days of bed rest and continuation of the prior regime, her weight decreased to 104¼ lb. Seventy mg. of lyohydrochlorothiazide was administered at this time, with a loss of 1¼ lb. Four days later an injection of 2 ml. of meralluride resulted in a diuresis of 4¼ lb. During this four-day interval the patient showed no evidence of the delayed response to hydrochlorothiazide mentioned later.

One patient in this group not previously treated with diuretics showed a good response.

No toxicity or side effects were noted other than weakness in 1 patient after three days of drug administration. This patient had an acute myocardial infarction and could not be weighed, but daily urinary output indicated a good diuresis, and the serum chloride level fell to 84 mEq. This cleared promptly when the drug was discontinued.

GRADE II. There were 20 patients in this group: 7 with arteriosclerotic heart disease, 10 with rheumatic heart disease, and 1 case each of congenital heart disease, chronic cor pulmonale, and hypertensive heart disease.

One patient had not had previous treatment with diuretics and showed a good response. Of the remaining 19, all had received diuretics previously with a satisfactory response, though the congestive heart failure was not completely controlled in all cases. Seventeen of the 19 patients showed a good response with a weight loss of 1 to 27 lb. after hydrochlorothiazide was started, the average weight loss being 7 lb. Thus, 18 of the 20 patients had a satisfactory diuretic response. Four patients previously maintained on chlorothiazide as the sole diuretic were felt to have an improved diuresis with hydrochlorothiazide.

Case 2. A. D., a 73-year-old woman with arteriosclerotic heart disease, chronic atrial fibrillation, and

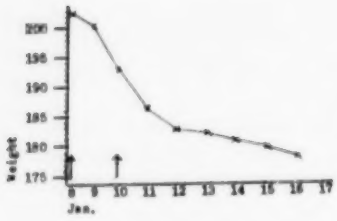

FIG. 1. Weight loss in L. D., a 46-year-old white man (case 3). Arrows indicate intravenous dose of 50 mg. of hydrochlorothiazide.

chronic congestive heart failure, was followed in the outpatient department. Her passive congestion was incompletely controlled on a 1 Gm. salt diet, digitoxin, 0.1 mg. daily, chlorothiazide, 500 mg. twice daily three days each week, and ammonium chloride. Hydrochlorothiazide, 50 mg. twice daily, was substituted for the chlorothiazide three days each week with a prompt loss of 6½ lb. and considerable improvement in the hepatomegaly and edema, though she still was not at a dry weight.

In several cases, a prolonged diuresis with a delayed maximal response was noted, particularly after intravenous administration. To our knowledge, this has not previously been reported.

Case 3. L. D., a 46-year-old white man, was admitted to the hospital on Dec. 31, 1958. For two years prior to admission he had had increasing dyspnea on exertion, cyanosis, ascites, and pedal edema. There was a life-long history of bronchial asthma. Previous treatment included a low-salt diet, digitalis, and intermittent injections of mercurial diuretics.

Cardiac catheterization showed no evidence of a shunt. Diagnoses of chronic cor pulmonale, obstructive emphysema, and congestive heart failure were made.

The patient was continued on digitoxin and a 1 Gm. salt diet. During the first week, with bed rest and 2 injections of mercaptomerin, he lost 14 lb. by diuresis. On Jan. 8, 1959, the patient weighed 202¾ lb.; he was given 50 mg. of lyohydrochlorothiazide intravenously. The next morning he weighed 200¼ lb., and the day after that, 192½ lb. The same intravenous dose was repeated, and during the next four-day period, he lost an additional 13 lb. by diuresis (fig. 1).

Two patients in this group responded poorly to hydrochlorothiazide in a dosage of 100 mg. daily. A larger dosage might have proved effective, though we have found that if the patient will respond at all to the drug, some effect can usually be obtained at this dosage level.

Nausea and weakness occurred in 1 patient of this group, who asked that the drug be discontinued. Serum electrolytes in this case were normal. Weakness and anorexia were noted by a second patient, but drug withdrawal was not necessary. Mild to moderate degrees of hypochloremia were not uncommon, but caused no untoward effects. No cases of hyponatremia or hypokalemia were noted in this series, but these complications have been observed by the authors since preparation of this report.

GRADE III. Four patients with severe, resistant congestive heart failure were given a trial of hydrochlorothiazide. Three had advanced arteriosclerotic heart disease and 1 had rheumatic heart disease. All had developed refractoriness to mercurial diuretics and chlorothiazide and showed no response to hydrochlorothiazide. Two patients subsequently showed some response to mercurial diuretics when started on large dosages of triamcinolone.

No toxic effects directly attributable to hydrochlorothiazide were noted in these

seriously ill patients. One developed paroxysmal ventricular tachycardia 12 hours after receiving 50 mg. of hydrochlorothiazide intravenously. This converted readily during the administration of 40 mEq. of potassium in 500 ml. of 5 per cent glucose in water. There were no other signs of possible digitalis toxicity; serum electrolyte determination at the time showed only a mild hyponatremia (sodium, 127 mEq.). The relation to hydrochlorothiazide therapy is conjectural.

COMMENT

Both chlorothiazide and hydrochlorothiazide cause a marked excretion of sodium, chloride, and potassium in the urine, apparently because of their renal tubular blocking action on the reabsorption of these ions. Chlorothiazide causes marked sodium loss and somewhat less chloride loss, while hydrochlorothiazide also produces a marked loss of sodium and a somewhat greater chloride excretion.[4] The excretion of potassium appears to be approximately the same with the two drugs.[2] There appears to be a greater bicarbonate excretion with chlorothiazide. The saluretic effect is greater and more prolonged with hydrochlorothiazide at a comparable oral dosage.[3] The latter effect was noted over a protracted period in one of the cases in this report (case 3). Both agents appeared to work better when acid salts, potassium chloride and/or ammonium chloride, were used as adjunctive therapy in this series. They were somewhat less effective when serum chlorides were at slightly depressed levels and much less effective when they were at moderately depressed levels; that is, when serum chlorides were depressed, after intensive or prolonged therapy, to less than 97 mEq., the diuretic responsiveness appeared to decrease.

Both drugs are well tolerated orally, are almost totally devoid of gastrointestinal intolerance even in the most advanced cases of congestive heart failure with severe visceral congestion. They remain consistently effective without evidence of drug tolerance developing and subsequent need of increasing the dosage. Mild erythematous skin rashes have been observed in approximately 2 per cent of our patients treated with chlorothiazide, but none were encountered in this series with hydrochlorothiazide. No adequate opportunity has been afforded to test the latter drug in a patient sensitive to chlorothiazide. To date, after two years of use, there has not been a single case of renal tubular degeneration because of any toxic effects of chlorothiazide. Hydrochlorothiazide has also not produced any toxic renal disturbance since its use was begun. Jaundice with the use of chlorothiazide has been reported[3] and was thought to be of the intrahepatic obstructive type. One of the authors (J. W. K.) has observed 2 cases of jaundice after prolonged use in severe advanced heart failure; 1 of these was fatal and appeared to be of a true toxic hepatocellular degenerative type (unreported), the other appearing to be of a reversible nature, clearing after cessation of chlorothiazide therapy and reappearing after the drug was restarted and administered a second time for approximately two weeks.

The greatest danger and toxic effect appears to be severe electrolyte depletion. Mild hypochloremia is a natural consequence of the use of these two agents, but if large dosages are given for too long a period in salt-depleted patients, severe hypochloremic alkalosis, "salt-depletion syndrome," and severe hypokalemic effects may

be produced. The adjunctive use of potassium chloride and/or ammonium chloride orally can prevent severe hypokalemia or hypochloremia, and in our opinion, they should be given whenever large dosages of both drugs are employed, particularly for long periods. If severe liver impairment is present, as is so often the case in long-standing congestive heart failure, loss of potassium may already have occurred and will be aggravated by this type of diuretic therapy. The depletion of potassium will lead to augmented digitalis effects with typical manifestations of digitalis intoxication, mild to severe, manifested often by unusual digitalis arrhythmias. The authors suspect that 1 of the cases reported here was caused by this effect.

It is recommended that regular serum electrolyte determinations be obtained when there is prolonged administration in advanced chronic congestive heart failure, particularly when hepatic or renal disease is suspected or known to exist; other patients should be checked at the slightest suspicion of electrolyte depletion, for example, if there is sudden oliguria or failure to respond.

Hypochloremic alkalosis usually responds promptly to the use of ammonium chloride. The response may be hastened by the combined use of a carbonic anhydrase-inhibiting agent for several days.

Both chlorothiazide and hydrochlorothiazide represent a significant advance in the diuretic management of congestive heart failure, approaching the effectiveness of parenterally administered mercurials. Their decided advantages are: effective oral administration, low incidence of toxicity, high patient acceptance, and sustained diuretic action over prolonged periods.

SUMMARY

Chlorothiazide and hydrochlorothiazide were administered to separate series of patients with congestive failure. Both drugs were potent oral diuretic agents for the short- and long-term management of these patients. One of these drugs (hydrochlorothiazide) was also effective by intravenous administration. Dosage and toxicity of the two drugs are discussed.

ACKNOWLEDGMENT

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BIBLIOGRAPHY

1. Novello, F. C., and Sprague, J. M.: Benzothiadiazine dioxides as novel diuretics (Communications to the Editor), J. Am. Chem. Soc. 79:2028-2029, April 20, 1957.
2. Stone, C. A., and Peck, H. M.: Hydrochlorothiazide, Preclinical Evaluation, West Point, Pa., Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., 1958.
3. Dreyup, A. L., Alexander, W. A., Lumb, G. D., Cummins, A. J., and Clark, G. M.: Jaundice occurring in a patient treated with chlorothiazide, New England J. Med. 259:534, Sept. 11, 1958.
4. Moyer, J. H., Fuchs, M., Irie, S., and Bodi, T.: Some observations on the pharmacology of hydrochlorothiazide, Am. J. Cardiol. 3:113, Jan., 1959.

DOUBLE CLEFT LIP. A new two-stage operation for the repair of double cleft lip is started when the infant is only 2 weeks old and completed two months later, it was reported at the recent meeting of the American Association of Plastic Surgeons in Boston. The abnormally prominent premaxilla is repositioned without surgery by gentle constant pressure from the repaired lip.

ALTITUDE AND ASTHMA. The thesis that altitude exerts a genuine physiological effect on asthma was supported by research at sea level and at 12,500 feet with guinea pigs, it was reported recently at the 15th Annual Congress of the American College of Allergists. Altitude-exposed animals in which asthma was induced had less severe asthma attacks. The work bears on the question of the extent to which psychosomatic factors are involved in treatment of asthma at altitude.

FROZEN BONE MARROW. Living bone marrow cells have been preserved successfully in a frozen state for use in persons exposed to radiation (Am. J. Nursing, April, 1959). Intravenous injection of the stored marrow produced "dramatic improvement" in the blood of 4 patients who had been receiving radiation therapy, reported Veterans Administration officials. The use of stored marrow may make it possible to treat patients much more intensively with radiation than was previously thought advisable.

ATARAXIC. Released recently is methoxypromazine maleate (Tentone, Lederle), designed to control psychic conditions that require more than a mild sedative but do not involve psychopathology. Minor side effects observed during clinical trials abated when dosage was reduced or stopped.

NEW SURGICAL PROCEDURE. A new surgical procedure to help laryngectomized patients to talk again creates an opening into the esophagus, using a small section of vein removed from elsewhere in the body, it was reported at the recent meeting of the James Ewing Society in New York City. Air taken in through this opening can be expelled through the mouth and used to form sounds.

SILICONE RUBBER. Animal experiments using silicone rubber, which resembles polyvinyl sponge, as a soft tissue substitute produced far less tissue reaction and fluid accumulation than did other synthetic materials, reported Francis A. Marzoni (Birmingham, Ala.) at the meeting of the American Association of Plastic Surgeons. The study suggests that silicone rubber may also be used to prevent unwanted bony union in surgery of the joints.

NEW ANTIHELMINTHIC. Pyrvinium pamoate, a cyanine dye, is very efficacious in eliminating pinworm infections in human beings, according to a report given at the recent Seventh Annual Meeting of the American Society of Tropical Medicine and Hygiene. A cure rate of 100 per cent was obtained with therapy given for seven days. Pyrvinium chloride was equally effective therapeutically, but seemed more toxic and was somewhat unpalatable.

TREATMENT FOR MYASTHENIA. Carotid sinus denervation as a surgical treatment for myasthenia was performed on 32 patients, with four complete clinical cures and 10 "fair to good" results, it was reported at the Second International Symposium on Myasthenia Gravis, held in Los Angeles recently. The surgery seems to be most successful in men in whom the disease began before age 35 and was not accompanied by thymoma. Only one clinical cure after surgery was reported among the women patients.

HEALING AND VITAMIN C. Animal studies have revealed that there is a direct relationship between the amount of vitamin C in the diet and the strength of healing wounds, it was reported at the meeting of the American Institute of Nutrition. The studies also showed a higher concentration of vitamin C in wound and scar tissue than in other muscle tissues. A single observation on a 30-year-old scar in a human being has also shown this higher concentration of the vitamin. Further studies are in progress to determine the exact metabolic role played by the antiscurvy vitamin in wound healing.

URICOSURIC AGENT. A new drug for gout reported to be four to six times as potent as other uricosuric agents is sulfinpyrazone (Anturan, Geigy). In patients observed for as long as one year, sulfinpyrazone maintained serum uric acid levels within normal limits. The new drug is reported to reduce the number and severity of acute seizures and to prevent the formation of new tophi; crystals already present are gradually dissipated through mobilization and increased urinary clearance.

Shakespeare's Psychiatry—and After*

Winfred Overholser, M.D., Sc.D., L.H.D.

SUPERINTENDENT, SAINT ELIZABETHS HOSPITAL, AND PROFESSOR OF PSYCHIATRY, GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
WASHINGTON, D. C.

We live in an age of psychology. Daily we read of mental mechanisms, of complexes, of the unconscious, of feelings of inferiority, of Freud and Jung, of psychosomatic medicine and, of ataraxics. There is a growing public appreciation of the facts relating to mental disorder and to normal mental functioning, while the care of the mentally ill in hospitals and clinics receives much attention from legislative bodies and the general public. Today the mentally ill are looked on as treatable, as sick, not of their own fault, and they are viewed with vastly greater compassion than was the case even 75 years ago.

In all ages men have been interested in human behavior and motivations and have attempted in one way or another to explain mental peculiarities. We flatter ourselves that we understand much more about the vagaries of human behavior than we did even a quarter of a century ago, but there certainly are still many gaps in our knowledge. If, with all our present understanding of psychology, of physiology and anatomy, of the effects of environment, early nurture, and heredity, we still have much to learn, what should we expect of the attitudes and knowledge in the time of Shakespeare, nearly 400 years ago? Just as today, there were then generally held beliefs on the nature, the causation, and the treatment of mental disorder. It seems appropriate on the occasion of this, the anniversary of the birth of the great dramatist, to review some of the notions that were prevalent in his day and that, like everything else that was of common knowledge then, were familiar to him. In Elizabethan times there was, of course, no such word as "psychiatry" and the related word "psychology" was invented by a German only in the latter part of Shakespeare's life (1590). The word psychiatry so far has been traced back to 1817, but it did not gain common currency until the close of World War I.

There is no question that in Shakespeare's time, as in all periods of human history, there were persons who behaved in such a peculiar manner that they were considered to be abnormal. Some of the conditions were looked on as proper subjects for treatment by the physician whereas others, particularly those thought to be due to demoniacal possession, were held to fall within the domain of the clergy. Various terms were applied to the victims of mental illness. They were referred to as maniacs, as melancholics, as suffering from phrenitis, frenzy, lunacy, or demoniacal possession. In viewing Shakespeare's delineations of madness and folly we must try to view them through the eyes of the medicine of that period. It is some of the medical ideas prevalent in his day that I would present to you here. As a preliminary warn-

* Presented at the Folger Shakespeare Library, Washington, D. C., on Shakespeare's birthday, April 23, 1958. The author is grateful to the staff of the Folger Library and to Miss Elizabeth Reavis, librarian of Saint Elizabeths Hospital, for their assistance in the preparation of this paper. This article is reprinted with permission from *Shakespeare Quarterly* 10, no. 3, summer issue, 1959.

ing against the "contemporization" of history, we may quote from Dr. Robert Willis, the translator of the works of Harvey:[1]

> The interpretation which successive generations of men give to a passage in a writer some century or two old is very apt to be in consonance with the state of knowledge at the time, in harmony with the prevailing ideas of the day; and doubtless, often differs signally from the meaning that was in the mind of the man who composed it. The world saw nothing of the circulation of the blood in Servetus, Columbus, Caesalpinus or Shakespeare until after William Harvey had taught and written.

Let us, then, try to assume for the nonce an Elizabethan state of mind and knowledge.

One branch of knowledge in Shakespeare's time had to do with astrology, that is, the influence of the planets on human affairs.[2, 3] The belief that the heavenly bodies influenced the lives of men and women is nothing new. It has a history—one to which there is no parallel—of 6000 years and was held in Mesopotamia, India, China, and ancient Greece, and in all of Europe during the Middle Ages and the Renaissance. Indeed, to the Elizabethan such a belief was entirely logical. The effects of the sun in furnishing light and warmth to the earth were manifest to all, and the waxing and waning of the moon and its influence on the tides were familiar. Why, then, should not the other planets have an effect on the earth and its inhabitants? In the philosophy of the time, the macrocosm, or universe, was inextricably linked with the microcosm, man. Even today, booklets purporting to give the horoscope of the curious purchaser based on the sign of the zodiac under which he was born are readily obtained, and in every large city one or more astrologers are listed in the telephone directory.

In Shakespeare's day belief in astrology was widespread, and although a few writers such as Bacon had attacked astrologers, they had done it on the basis of the trickery of the practitioners rather than on the basic truth or falsity of the alleged science. The conjunction and the opposition of the planets at the time of a man's birth influenced the proportions of the humors that were found in his body and therefore had to do with his temperament or "complexion"—choleric, sanguine, phlegmatic, or melancholic. Indeed, the course of a man's life and his death were influenced by the stars, and could be predicted. Chaucer, for example, said:[4]

> For in the sterres, clerer than is glas,
> Is writen, god wot, who-so coude it rede,
> The deeth of every man, withouten drede
> . . . but mennes wittes been so dulle,
> That no wight can wel rede it atte fulle.

Burton, author of the *Anatomy of Melancholy*, was said to be "an exact calculator of nativities" and reputedly predicted the date of his death by his horoscope. The planet Saturn, for instance, was looked on as malign and as tending to cause an excess of black bile, thus producing melancholy. Most of the arguments that were alleged against astrology were theological in nature, but obviously the whole doctrine could hardly be refuted as long as the geocentric astronomy of Ptolemy held sway. It is interesting to note that the sun and the moon were numbered with the other five planets (Saturn, Jupiter, Mars, Venus, and Mercury).

The personal physician to Henry VIII and Elizabeth I, Thomas Vicary,[5] believed in the influence of the moon and stars on the organs, and Dariot,[6] another physician, wrote a volume on astrology. Elizabeth I, likewise, retained as one of her advisers John Dee, a notorious astrologer, and apparently was much guided by his advice. Astrology purported to teach the Elizabethan to know his friends and enemies, to prepare him for the future, and indeed to answer every question. Not only could astrology predict the success in life of individuals, but the planets were thought to have much to do with the proper times for bleeding, for gathering medicinal herbs, or for preparing the soil for planting. Chaucer spoke of the Doctor of Physic among his Canterbury pilgrims who was "grounded in astronomye" and "wel coude . . . fortunen the ascendent of his images for his pacient." In the time of Shakespeare as well, astrology played an important part in the training of the physician; the balance of the humors, the outcome of the disease, and the nature of the herbs to be used in treatment were influenced by the planet under which the patient was born. Burton[7] quoted Paracelsus as opining that a physician without the knowledge of stars cannot "either understand the cause or cure of any disease, either of this, or gout, nor so much as toothache; except he see the peculiar geniture and scheme of the party affected." He added that "the constellation alone many times produceth melancholy, all other causes set apart." He gave instance "in lunatic persons that are deprived of their wits by the moon's motion," but added, however, that the stars "do but incline and that so gently, that if we will be ruled by reason they have no power over us; but if we follow our own nature and be led by sense they do as much in us as in brute beasts and we are no better." Sir Thomas Browne, the eminent physician, warned, "Do not reject or condemn a sober and regulated Astrology; there is more truth therein than in astrologers . . .; we deny not the influence of the Stars."[8]

Burton and Browne wrote soon after Shakespeare's death, although their views were those in vogue earlier; for example, Boorde[9] spoke of "a lunatic which will be ravished of his wits once a moon, for as the moon doth change and is variable so be those persons mutable and not constant witted." Again, Vicary[5] said (p. 17):

> Also the brain hath this property that it moveth and followeth the moving of the moon; for in the waxing of the moon the brain followeth upwards, and in the wane of the moon the brain descendeth downwards and vanisheth in substance of virtue, . . . and this is proved in men that be lunatic or mad . . . and also in men that be epulentic or having the falling sickness, that be most grieved in the beginning of the new moon and the latter quarter of the moon.

It was generally believed, then, that the phases of the moon had much to do with mental illness, perhaps in causation but certainly in aggravation and amelioration. Webster, in his Duchess of Malfi, for instance says, "Madmen act their gambols to the full of the moon."

Shakespeare was familiar with the terms "lunacy" and "lunatic" and with these other notions concerning the astrological influence on behavior. Indeed, he made more than 100 astrological allusions in his plays and sonnets, although he did not once use the word "astrology", instead he used "astronomy" consistently. Whether or not he believed in astrology is, however, an academic question. At any rate, we

may be sure that Shakespeare's listeners were familiar with astrological beliefs and that mention of such beliefs struck a responsive chord. For Shakespeare, said Wedel,[10] "astrology was principally a convenient source for figures of speech."

The influence of the planets, then, was considered to be one of the factors in what passed for psychiatric etiology in the Elizabethan period. Another factor was the supernatural, as exemplified in witchcraft.

In Shakespeare's day the belief in witchcraft was universal, not only in England and Scotland, but on the Continent.[11–18] Indeed, the excesses of the witch hunters in England and Scotland were relatively mild compared with the savagery exhibited in France and Germany. The belief in the power of the supernatural and its mediation by human beings stems from scriptural days; it was thought that to deny witchcraft was practically to be an atheist. By the time of Henry VIII, witchcraft, formerly punished, usually with penance, by the ecclesiastical courts, had been taken under the jurisdiction of the civil courts, and those convicted of witchcraft were often executed as criminals. In 1563, under Elizabeth I, a statute was enacted decreeing imprisonment for the first and death for the second offense of sorcery or any damage to property or persons by means of witchcraft; by the time of James I, in 1604, a still more rigorous law was passed. Estimates vary as to the number of persons executed on charges of practicing witchcraft; in the time of James I, nearly half of all persons accused of witchcraft were hanged, and the numbers were in the thousands. Indeed, Matthew Hopkins, the "witch-finder," himself hanged in 1647, alone caused the death of more than 4000 witches! Such trials and executions were far from uncommon during Shakespeare's lifetime and for a long period thereafter. This belief in the power of witches to do evil had a bearing, *inter alia*, on the interpretation of mental symptoms.

The witch, or less often the wizard, was in a compact with the devil, had power to evoke the devil and various spirits and through their power to cause damage, illness, and death. Glanvil[19] said, "A witch is one who can do or seems to do strange things beyond the known power of art and ordinary nature, by virtue of a confederation with evil spirits. The strange things are really performed and are not all impostures and delusions." Whatever baffled the physician in the line of illness was conveniently ascribed to witchcraft, just as today we hear of bacteria, viruses, allergies, and "psychosomatic" illness. Many physical complaints such as sudden illnesses were laid to this cause, and fits, with or without loss of consciousness, were thought to be almost characteristic of bewitchment.* Some of the alleged victims vomited pins and nails, and there was much speculation as to how these foreign bodies were introduced into the body of the subject. Actually, the fits, the vomiting of the pins, and the rest were largely due to an hysterical desire for attention by the highly suggestible, or the result of direct imposture. Not only human beings were the object of the witches' machinations; animals sickened and died, storms were brewed, fires were caused. The witches could summon spirits, who in the form of

* The following quotation is apropos: "As the modern reader glibly interprets human conduct in terms of Freud, Jung, or whosoever may be his pet theorist, so the Tudor and Stuart citizen found satisfactory explanations in Bright, Walkington, Huarte, Charron and other writers who elucidated the always interesting question of the reason's for man's behavior."[20]

succubi and incubi had carnal relations with human beings, or could cause impotence, sterility, or abortion. Witches, too, could bring about apparitions, could leave the room through a keyhole and go to distant places, or by the use of ointments make themselves invisible. The idea of the witches' Sabbath was much more common on the Continent than in England, but many strange tales were told by witches in their alleged "confessions," e.g., that they had attended revelries at which they had sexual relations with devils and perhaps even engaged in cannibalistic activities. These confessions, as we read them today, are obviously the expression of delusions entertained by psychotic persons or statements extorted by severe torture. In short, almost any evil was attributed to the activities of these witches through their confederacy with the devil.

The *modus operandi* of bewitching was explained by Sir (Dr.) Thomas Browne,[21] one of the best known physicians in the Stuart period, during a trial of witches in 1665:

> . . . That the devil . . . did work upon the bodies of men and women upon a natural foundation, [that is] to stir up and excite such humors super-abounding in their bodies to a great excess, whereby he did in an extraordinary manner afflict them with such distempers as their bodies were most subject to . . . these swooning fits were natural, and nothing else but that they call the mother [hysteria], but only heightened to a great excess by the subtility of the devil, cooperating with the malice of those which we term witches, at whose instance he doth these villainies.

Another type of difficulty was supposedly caused by the witches, namely, the form of mental illness or madness known as demoniacal possession. King James I,[22] in his *Demonology* said,

> They [the witches] can make folks to become phrenetic or maniac, which likewise is very possible to their master to do, since they are but natural sicknesses. And likewise they can make some to be possessed with spirits and so to become very demoniacs, and this last sort is very possible likewise to the devil their master to do, since he may easily send his own angels to trouble in what form he pleases any whom God will permit him so to use.

One of the four general types of madness was called demoniacus, which Boorde, in his *Breviary of Healthe*, said is caused by the possession of the devil and is "worse than the maniac." He told of a German woman who was brought to Rome while he was there and who was exorcised at St. Peter's. He commented that she must do penance or she will have eternal punishment and added, as to the demoniacs, that "no man can help them but God and the King"[9] (book 2, *Extravagantes*, folios 5 and 7). If they did not respond to exorcism and prayer they were likely to be subjected to torture and imprisonment. It seems likely that when Shakespeare used such expressions as "He is sure possessed, Madam" (*Twelfth Night*), or "How long hath this possession held the man?" (*Comedy of Errors*), or "For nature so preposterously to err sans witchcraft could not be" (*Othello*), he was using something more than a mere figure of speech. We may note, too, that the witches in *Macbeth* have beards and disappear suddenly—two marks of the true witch.

Many volumes have been written on witchcraft in old England and America, as well as on the Continent, but time does not permit a full discussion of this interesting and tragic popular delusion. We should add, however, that there were those who

spoke out against this belief. One of the most powerful of these was Johannes Weyer of Germany, a student of Henry Cornelius Agrippa.[23] Reginald Scot,[24] in England, based his attack on witchcraft largely on Weyer's writings. Neither Weyer nor Scot nor the few others who dared to speak out against witchcraft, however, denied the existence of spirits or the possibility that human beings could make compacts with spirits. Sir Thomas Browne[25] said in his *Religio Medici*,

> For my part I have ever believed and do now know that there are witches. They that doubt of these do not only deny them but spirits and are obliquely and upon consequence a sort not of infidels but atheists. . . . I could believe that spirits use with men the act of carnality and that in both sexes. . . . I hold that the devil doth really possess some men, the spirit of melancholy others, the spirit of delusion others.

The *Malleus Maleficarum*[26] (1490), which may be referred to as the bible of the witch hunters, devoted a whole chapter to the method by which devils through the operations of witches sometimes actually possess men. Zilboorg has well said that if in reading this volume we substituted the word "patient" for "witch," we should have a veritable textbook of psychopathology.

Partly under the influence of physicians like Cotta[27] and clergymen like Bekker[28, 29] and Hutchinson,[30] the witch mania gradually subsided about a century after Shakespeare, the last execution, indeed, occurring in 1684 in England. There was an execution in Scotland in 1711 and in 1712 a conviction in England, which, however, resulted in a pardon. Finally, in 1736 prosecutions for witchcraft were forbidden by an act of Parliament. This act, interestingly enough, is still in force, and as recently as 1944 (R. v. Duncan, 2 [1944] All E.R. 220) a conviction was had under it on the charge of "pretence to conjuration contrary to the Witchcraft Act." The court pointed out that the law does not refer to conjuration of evil spirits only but that it is the pretense that is the gist of the crime. At the time this Witchcraft Act was passed it may be noted that John Wesley, among others, lamented the decadence of a belief in witches. Indeed, he thought that giving up this belief was almost equivalent to giving up the Bible itself!

Passing from this topic we may say in summary that belief in witchcraft, like belief in astrology, was prevalent in the time of Shakespeare; it certainly affected the interpretation of mental phenomena by the public and very likely as well by Shakespeare himself.

So far we have considered what may be termed the extraneous influences that played on man and influenced or governed his behavior and, indeed, his destiny. What of the anatomical and physiological beliefs of the time? How did the human organism function? Essentially, the beliefs were those that had been handed down from Galen, about A.D. 200. During the whole of the Dark Ages and of the Middle Ages his teachings had acquired almost the standing of a religious dogma, and to doubt what Galen had said about the structure or the function of the body or the treatment of its diseases was almost tantamount to heresy. Some brave souls, however, had dared to investigate and to doubt. Vesalius, by his careful dissections, had disproved many of the anatomical errors of Galen (1543), in the same year, indeed, that Copernicus had begun the demolition of the geocentric basis of the existing astronomy. Harvey, the discoverer of the circulation of the blood, thought it wise

to have the first edition of his work (1628) published in Germany rather than in England. He may have remembered what happened to Galileo and been mindful of the fact that Servetus, the discoverer of the pulmonic circulation, had been burned at the stake on Calvin's orders, even though it was actually for his theological views rather than for those on physiology!

The fundamentals of physiology, as they were still known in the time of Shakespeare, were briefly as follows:[31] The basic principle of life was known as the spirit or pneuma and was drawn from the world spirit in the act of breathing, entering through the trachea into the lungs and then by way of what we now call the pulmonic vein to the left ventricle. Food was carried as chyle to the liver (the "shop of blood," as Lemnius[32] called it) by the portal vein. It was there converted to blood and endowed in some unexplained way with natural spirit; this bestowed the power of growth and nutrition. Part of the blood was supposed to go to the right side of the heart, where it gave off its impurities by way of what we now call the pulmonic artery, these being exhaled through the lungs. The venous blood, thus continually purified, ebbed to and fro in the veins for nutrition. A small part of this blood passed through invisible pores into the left ventricle, where it was mixed with air, thus becoming arterial blood and charged with vital spirit. This moved to and fro in the arteries, giving the function to the organs. If it reached the brain it became charged with the third kind of spirit, the animal spirit. This was carried from the brain through the nerves (which were thought to be hollow) and initiated the higher functions such as motion and sensation. According to the generally accepted scheme of things, there were four elements, namely, earth, cold and dry, water, cold and moist, air, hot and moist, and fire, hot and dry. These in turn were influenced by the humors, also four in number, these being blood, choler or yellow bile, phlegm, and black bile. Depending on the mixtures of the elements and the proportion of the humors in the body, there were various complexions or temperaments named after the humors, the sanguine, the phlegmatic, the choleric, and the melancholic—words that are in common speech today as indicating the general temperament of individuals. If there was an equal counterpoise and balance of the elements and the humors, the person was said to be "well-tempered," but if one predominated then he was "ill-tempered." Again, if the humors were in good balance the individual was "in good humor." It was this balance of the elements that Shakespeare had in mind when he made Antony say of Brutus:

> His life was gentle, and the elements
> So mixed in him, that Nature might stand up,
> And say to all the world, "This was a man!"

Burton, in his *Anatomy of Melancholy*, defined a humor as "a liquid or fluent part of the body comprehended in it for the preservation of it, and is either innate or born with us, or adventitious and acquisite"[7] (p. 128). It is of some interest that within the last few years or so there has been a recurrence of the use of this term by neurophysiologists, who now speak of neurohumors.

Depending on the predominance of one humor or another there were characteristic physical and psychological types. The sanguine man, for example, was handsome

physically, had a happy outlook on life and considerable charm of personality. He was also, however, subject to violent lusts and passions and ran the risk of unrequited love, which might then give him melancholy. The choleric man, particularly the one born under Mars, was violent and shameless or else deceitful and conspiring; like Cassius in *Julius Caesar*, he might have a "lean and hungry look." The phlegmatic type was fond of luxury, and if he had been born under the moon he might be a fool and a coward. The melancholy type was the one of which we read the most in Elizabethan literature. The first book by an English physician on mental diseases, Timothy Bright's *Treatise on Melancholy*, first published in 1586, which was probably well known to Shakespeare, was devoted entirely to the subject. Burton's *Anatomy of Melancholy* dealt exhaustively with the topic. Of Burton's work Sir William Osler[33] said, "[It] is a great medical treatise, orderly in arrangement, serious in purpose, and weighty beyond belief with authorities." Although it did not appear until five years after Shakespeare's death, it is an *omnium gatherum* of the literature on the topic back to classical times; it certainly represents most of the views on mental disorder that prevailed in the Elizabethan period.

The melancholic man was supposed to be lean, with hard skin and dusky color, subject to various physical diseases and numerous psychological hazards. In general he slept badly, had fearful dreams, was timorous, full of fear, doubt, and distrust, and one whom "nothing can please but only discontentment." Walkington[34] spoke of the man of melancholic complexion as either God or demon and added, "He is like a huge vessel on the rolling sea. It is either hoist up to the ridge of a main billow or else hurried down to the bottom of the sea valley"—a very suggestive passage, indicating that even in Shakespeare's day it was recognized that the alternating elation and depression of what today we call the manic-depressive temperament were not unusual. Du Laurens[35] said that melancholy men are witty, since "the humor causeth the divine ravishment or enthusiasm which stirreth men up to play the philosopher, poet, and also to prophesy." It was generally believed also that the melancholy individual was particularly subject to demonic influence. Juan Huarte[36] wrote that Aristotle said that all men who signalized themselves in science were melancholic; in his opinion the melancholic humor was the cause of integrity and constancy. This humor, which is hot and dry, he said, "gives us courage, pride, liberality, audacity, cheerfulness, and pleasantness." Thus, it seems that the person possessed of what was termed "natural melancholy" had some very useful traits. Perhaps it is for this reason that we read in Elizabethan literature much more about this type of person than any other. Indeed Professor Lawrence Babb[37] has written a comprehensive study, entitled *The Elizabethan Malady*, concerning the way natural melancholy was treated in the literature of the time.

There were cases, however, according to the writers, in which melancholy became "unnatural," that is, a form of mental illness, along with mania, phrenitis (the type of mental illness with fever or, as we should say today, delirium), demoniacal possession, and lunacy (the type occurring once in a moon). Du Laurens discussed dotage, which was the general term for mental illness. "This," he said, "occurs when some of the principal faculties of the mind, as imagination or reason, is corrupted. . . . All melancholy persons have their imagination troubled." This condition is

usually without fever because the humor is dry. If the humor becomes shut up in the ventricles of the brain, however, it causes falling sickness (epilepsy). In the melancholy dotage without fever, the patient has for his ordinary companions "fear and sadness without any apparent occasion. . . . Dotage with fever if continued is called frenzy through inflammation of the brain and its membranes or of the muscles called *diaphragma* or *phrenos*"[13] (p. 87). Under certain circumstances this or any of the other humors might become overheated, burned, or, in the Elizabethan term, "adust."

Of the types of mental disorder not clearly due to extraneous influences, particularly of a supernatural nature, it was generally agreed by the writers of Shakespeare's time that the brain was at fault in cases of madness. Shakespeare, indeed, used the phrase "brain-sick" several times, as in referring to "the bedlam brain-sick duchess" (*Henry VI*, part 2).

Another physical symptom of madness was thought to be the pulse, which was irregular or rapid (as it might well be in an excited patient). It is to this that Hamlet refers, for instance, when he says, "my pulse, as yours, doth temperately keep time," in attempting to prove that he is not truly mad. In other words, the Elizabethans interpreted mental illness largely on an organic basis. They described three cells of the brain, or ventricles, the anterior one being the seat of imagination, the middle one of reason, and the posterior one of memory. Although a certain amount of compartmentalization was supposed, it is interesting that Huarte at least stated that all three faculties are united in each ventricle, thus anticipating the doctrine of the unity of the organism. The fourth ventricle was said to digest and refine the vital spirits and turn them into animal spirits, thus enabling them to give sense and motion to all parts of the body. Huarte made the comment that it is fortunate that the liver is so far from the brain "lest by the noise of the boiling and concoction of the food and obscurity and clouds cast on the animal spirits by the vapors, the rational soul should be discomposed in reasoning"[18] (p. 130).

The causes of unnatural melancholy were numerous and various. Batman upon Bartholome,[7] for example, listed "melancholy meats, strong wine that burneth the humors, passions of the soul, great study, the biting of a woode hounde (mad dog) or some other venomous beast, corrupt and pestilent air and corrupt humor." Various types were described too, such as head melancholy, love melancholy, religious melancholy, widows' and nuns' melancholy, and the windy (flatulent) melancholy or hypochondriasis. As for the symptoms, Boorde[9] (folio 78) wrote that the sickness is full of fantasies, "Thinking to hear or see. The patient may think himself God or that he is about to be damned." Other symptoms described are suspicion, watchfulness, sighing, restlessness, and fearful dreams. The patient shuns the light, "for humors are contrary to light." The picture of unnatural melancholy is, indeed, not unlike the clinical picture seen in depressions with a certain amount of agitation, then, as now, the danger of suicide was recognized. We read more of melancholy than of the other types of mental illness in the Elizabethan literature, and relatively few descriptions of the actions of the maniac, of the phrenetic, and of the demoniac are found. References to lunatics are found, particularly in connection with bedlam, of which more later. The outlook for these mental conditions was rather guarded.

Boorde, for instance, wrote[4] (folio 65) that "madness may come by nature and kind and then is incurable, or else it may come by great fear or great study." Presumably, in the latter type the outlook is better. He continued: "Frenzy is with fever, so is not mania or madness. [Madness] comes of a corrupt blood in the head or of a bilious blood intrused in the head, or weakness of the brain which letteth [prevents] a man to sleep or turning upso down of the head which doth make the madness."

Many of the milder cases were cared for outside of Bedlam, usually in the home, and the books are full of descriptions of the various sorts of treatment that should be given. First, since the condition was due to a perturbation of the humors, it was important that the patient should be relieved of them as much as possible. Consequently, we find bloodletting frequently prescribed, as well as various purges upward (that is, emetics) and downward. Burton wrote[2] (p. 383) that it was the common practice of some men to go first to a witch and then to a physician. "Thus," he wrote, "if they cannot bend Heaven they will try hell." "If a disease is caused by incantation," he wrote, "it must be cured by it," although, he added, others object to this statement. He wrote likewise of exorcisms, fire, suffumigation, lights, cutting the air with swords, and herbs and odors. Since the external senses are doors for impressions from the outer world, a pleasant house and apparel, music and pleasant sights, good studies and exercises were recommended.

Bright[39] wrote of ornamentation, of precious stones "which have a virtue against vain fears and baseness of courage," such as the carbuncle, chalcedony, ruby, and turquoise. He added, "As for furious melancholy, I leave it to be cured as disease and sickness." Diet was considered to be important, since what was taken into the stomach affected the "decoction of the humors in the liver." Broths and sirups, for example, would moisten the humors. Various kinds of exercise were also prescribed.

As for the various remedies that were used, they were almost literally legion. Indeed, Burton devoted more than 40 pages to the topic of medicines. He evidently had some doubt in spite of all of this consideration, for he remarked that "Many an old wife doth more good than our bombast physicians," and again, concerning the different prescriptions of various authorities, he wrote, "But each man must correct and alter, to show his skill, every opinionative fellow must maintain his own paradox, be it what it will; the Kings rage, the Greeks suffer, they dote, and in the meantime the poor patients pay for their new experiments, the commonalty rue it." Although various precious stones and gold were sometimes used, the greatest emphasis was laid on herbs and simples. Polypharmacy was certainly popular. Mithridates, electuaries, apozemes, and other compounds contained a huge number of constituents, so many, indeed, that Burton well remarked[2] (pp. 563–606, especially pp. 563 and 571), "Three hundred simples in a julip, potion, or a little pill, to what end or purpose?" As an example, consider the recipe for an apozeme (decoction) given by Du Laurens[35] (p. 159):

> Take of the roots of bugloss and elecampane, of the rinds of the roots of capers and tamarisk, of everyone an ounce, of the leaves of borage, hops, succory, fumitory, capillus Veneris, crops of thyme and balm, of each a handful, of anise, fennel, and citron seed, of each two drams, of the three cordial flowers, of the flowers, of oranges and epithymum, of each a pugill, boil them all in fountain water, and after you have strained out a pound and a half, put thereto

> of the syrup of hops two ounces, and as much of the syrup of fumitory, and make thereof an apozeme, clarify it and aromatize it with a dram of the powder of cinnamon or of electuarium de gemmis, it must be taken four mornings together.

Many of the herbs used have little or no medicinal value, and the names of most of them are strange to us today, such as betony, borage, bugloss, and carduus benedictus. Others, like hops and marigold, are familiar to us in other connections. Black hellebore, recommended by the Greeks, was still in use in Shakespeare's time. Burton noted, "It was generally so much esteemed of the ancients for this disease among the rest that they sent all such as were crazed, or that doted, to the Anticyrians, . . . to be purged, where this plant was in abundance to be had. In Strabo's time it was an ordinary voyage, sail to Anticyra, a common proverb, to bid a dizzard or a madman to take hellebore." Another drug mentioned by Burton, although it is not found anywhere in Shakespeare's works, is tobacco, which had been introduced by Sir Walter Raleigh. Wrote Burton[7] (pp. 577, 579):

> Tobacco, divine, rare, supercxcellent tobacco, which goes far beyond all their panaceas, potable gold, and philosopher's stones, a sovereign remedy to all diseases. A good vomit, I confess, a virtuous herb if it be well qualified, opportunely taken, and medicinally used; but as it is commonly abused by most men . . . 'tis a plague, a mischief, a violent purger of goods, land, health, hellish, devilish and be damned tobacco, the ruin and overthrow of body and soul.

Tobacco, or henbane of Peru, is described in Gerard's *Herball* and is said to ease migraine and fits of the "mother." Gerard added, "It purges up and down." One author, de Lancre (1612),* accused witches of using tobacco, presumably to facilitate their trances, adding, "it makes their breath and bodies stink." With regard to the question of the fits, it should be mentioned that the "mother," the matrix or the uterus, was thought to move up and down during a fit, thus causing suffocation and various symptoms that today we know under the name of hysteria. Shakespeare referred to this condition in King Lear: "Oh, how this mother swells up toward my heart. Hysterica passio! Down, thou climbing sorrow, thy element's below." One other drug is worthy of mention, namely, the mandrake or mandragora. Gerard wrote that there are many ridiculous tales about this herb, that it is said that when it is pulled from the earth it shrieks and that the roots have the shape of a man or a woman. "It hath drowsy and sleeping powers," he wrote.[1] Shakespeare had Iago say, for example:

> Not poppy nor mandragora
> Nor all the drowsy syrups of the world
> Shall ever medicine thee to that sweet sleep
> Which thou ow'dst yesterday.

As for the results of these drastic medications, statistics are not available. Evidently some patients at least survived!

What of the mentally ill who were so disturbed that they appeared to need in-

* Quoted by Dickson.[10] Dickson referred to de Lancre as a "demonographer extraordinary" and persecutor of witches.

stitutionalization?[12] In Shakespeare's time there stood near the Bishop's Gate without the city wall of London a hospital, or asylum, for the mentally ill. Founded in 1247 as the Priory of St. Mary of Bethlehem, the hospital had from 1377 on been used for the care, or at least the confinement, of mad, lunatic, and distracted persons. The name soon became corrupted from Bethlehem to Bethlem and thence to Bedlam, thus adding a picturesque and vivid word to the language. From the early days the institution was referred to as a hospital, but that fact should not mislead us into picturing it as having any resemblance to one of our modern establishments. The unfortunate persons who were sent there were the more obviously deranged, but once they had entered within those walls they were looked on as objects of scorn and derision. It is of interest as reflecting Shakespeare's humane attitude toward the mentally ill that in contrast with his contemporaries such as Peele and Middleton, he rarely used the mentally deranged for comic relief. In employing the fool for comic purposes as he did, he was, of course, following the stage tradition of his times. Furthermore, the fool was a professional, and was often far from being mentally retarded.

In Bedlam the sexes were mingled; no attempts were made at any sort of sanitation, heating, or proper feeding. It was reported in 1631, for example, that the patients had had nothing for days but scraps, and "were like to starve." The inmates were chained and often whipped, kept in dark cells, and used as objects of entertainment for the public, who were allowed to visit for a fee.

Sir Thomas More wrote of a man who had been put into Bedlam and afterward "by beating and correction had gathered his remembrances to come again to himself." When the patient relapsed and made something of a nuisance of himself, the chancellor caused him to be bound to a tree in the street before the whole town, while constables "striked him with rods 'til they waxed weary." More added, "Verily, God be thanked, I hear no harm of him now." Again, in Dekker's play *The Honest Whore*, one of the characters says, "Yes, forsooth I am one of the implements. I sweep the madmen's rooms and fetch straw for 'em and buy chains to tie 'em and rods to whip 'em. I was a mad wag myself here once but I thank Father Anselmo. He lashed me into my right mind again." This scene is laid in the "Bethlehem Monastery near Milan" but obviously refers to the Bethlehem Hospital. Such treatment as the patients received, then, was a combination of cruelty and systematic neglect. Fortunate, indeed, was the victim who survived. Darkness, it may be added, was considered a cure for frenzy, since as Batman upon Bartholome[13] wrote (p. 88b), "It takes away the imagination that cometh by the sight."

A reference to the behavior and symptoms of the inmates is found in Lavater:[13] "madmen which have utterly lost the use of reason, or are vexed by God's permission with a devil . . . do marvelous things, talk of many visions and divers other matters. Their sight deceiveth them, insomuch as they mistake one man for another: which thing we see by experience, in Bedlam houses where mad and frantic men are kept."

Presumably the prevailing treatment of the institutionalized mentally ill was a matter of common knowledge; accordingly we find a number of references in Shakespeare's plays: Rosalind's remark that "love is merely a madness and deserves as

well a dark house and a whip as madmen," Romeo's comment that "he is bound more than a madman," and Pinch's advice that "they must be bound and laid in some dark room."

One of the stock characters in Shakespeare's time was "Tom o' Bedlam." From time to time the governors had to relieve the crowding at Bedlam by discharging patients whose cure was, to say the least, doubtful. Thrown upon the world, homeless and without friends, these patients wandered about the countryside chanting wild ditties and wearing a fantastical dress to attract the notice and the alms of the charitable. Some of their actions are described in Edgar's soliloquy in King Lear thus:

> . . . Bedlam beggars, who with roaring voices,
> Strike in their numbed and mortified bare arms
> Pins, wooden pricks, nails, sprigs of rosemary;
> And with this horrible object, from low farms
> . . .
> Sometimes with lunatic bans, sometimes with prayers,
> Enforce their charity.

Among the half dozen "mad songs" in Percy's[11] *Reliques** is one entitled, "Old Tom of Bedlam," which starts as follows:

> Forth from my sad and darksome cell
> Or from the deep abyss of hell
> Mad Tom is come into the world again
> To see if he can cure his distempered brain.

That songs of this sort were well known is indicated in a line from Ben Jonson's *The Devil is an Ass:* "Your best song's Thom o'Bet'lem." In another song with the same title, the subject sings that he has been

> In durance soundly caged
> In the lordly lofts of Bedlam,
> On stubble soft and dainty,
> Brave bracelets strong, sweet whips ding dong,
> With wholesome hunger plenty.[12]

These patients apparently had some sort of a license, or at least were permitted by custom, to go begging, and they wore about their necks a great horn. When they came to a house they would blow the horn and then put a stopple in it to contain the drink that might be given to them. This is apparently the reference in *King Lear*, "Poor Tom, thy horn is dry." So much was the "Bedlam begging" abused that in 1675 the governors of Bedlam found it necessary to announce[13] (p. 138) that no patients were discharged with a license to beg!

Bedlam was moved to a new building in 1674, and apparently steps were taken after that time to segregate the sexes. It is doubtful whether very much improve-

* Percy commented (p. 350): "It is worth attention, that the English have more songs and ballads on the subject of madness, than any of their neighbours. Whether it is that we are more liable to this calamity than other nations, or whether our native gloominess hath peculiarly recommended subjects of this cast to our writers, the fact is incontestable."

ment had come about, however, by the time Hogarth in the 1730's was making his etchings of "The Rake's Progress." His "Scene in Bedlam" is, of course, familiar to all. The beginning of humane care of the mentally ill in English hospitals dates from the founding of the York Retreat by the Quakers in 1792.

The question naturally arises, how much of astrology, of witchcraft, and of the humoral pathology did Shakespeare himself believe? It is difficult, if not impossible, to speak with finality on this question. He was perhaps the most accurate mirror ever held up to mankind, a keen observer, one who knew human nature, and who depicted it with truth. He was a dramatist, well attuned to the tastes and the knowledge of those who saw and would read his plays. He was, in every way, a man of his time. The general belief in the influence of the planets cannot have left him untouched, and yet it is significant that never once did he use the word "astrology." He resorted to witchcraft, witches, and ghosts only on rare occasions. From his writings we cannot estimate the extent to which he believed in the legends of his time.

As for a belief in the humoral pathology, there was no other pathology in his day. Galen's influence was still strong, even though Leonardo had ventured to doubt, and even though Vesalius had published his epoch-making studies of anatomy before Shakespeare's birth. The interesting speculation has been offered that Shakespeare knew something of the rumors of Harvey's work, even though the latter's studies of the circulation of the blood were not published until 12 years after Shakespeare's death. There are one or two references that may be used to bolster this speculation, but it is only speculation nevertheless.

As for mental illness, it seems reasonably clear that he viewed insanity, or madness, as a disease of the brain, due to various causes and possible of cure by medical means. Although he made reference to the dark room and the chains and the beatings, he nevertheless had the physician in *King Lear* resort to what today we would call prolonged sleep treatment for the successful cure of the ailing king. Shakespeare was a humane person and treated his mentally deranged characters with sympathy. His depictions of human nature and the struggles of human beings in the face of conflict and stress are vivid and show a rare understanding of mental mechanisms.

It is interesting too to note that some of the beliefs that prevailed in Shakespeare's time are not entirely dead even today. There are still those who believe in the power of the planets to influence human affairs and who consult astrologers for advice. As for witchcraft, there are areas of the United States where a belief in the power of "hexing" to bring about evil or curative effects on human beings and on animals still flourishes. As for the humors, the word is being used again in neurophysiology, although, of course, in a somewhat different sense from that which prevailed in the time of Shakespeare. Our everyday speech has been enriched by numerous words and phrases that originally referred to astrology, witchcraft, or the humoral pathology—consider, disaster, lucky stars, jovial, mercurial, saturnine, prestige, glamor, bewitch, choleric, splenetic, phlegmatic, sanguine, and melancholic, to mention only a few.

We have reviewed all too briefly some of the ideas prevalent in Elizabethan and

Stuart times relative to the mental functioning, particularly the abnormal, of human beings. In the space of 350 years it might be expected that much has happened in the field of psychiatry, and indeed, such is the case. Not only that, the progress in very recent years seems to be gaining speed, and to predict what may come about in the next 50 years would need a wise and rash man indeed. As knowledge has increased as to physiology and pathology, the need for reference to supernatural influences has waned. Diseases that were formerly ascribed to witchcraft we now know to be due to infections, new growths, or nutritional disorders. Although Michael Servetus (1553) had described the pulmonic circulation even before Shakespeare's birth and had been burned by order of Calvin for writing the book in which this discovery was announced, it was the revolutionary book of Harvey (1628) on the circulation of the blood that caused the first serious doubts concerning the humoral pathology. A few years later the theories of Harvey were completed by Malpighi's (1661) demonstration of the capillary circulation. The work of Boyle (1660), who demonstrated the weight of air and studied respiration and combustion, gave the *coup de grâce* to the humoral theories, although formal physiology was not developed until the time of Claude Bernard in the middle of the nineteenth century. Later developments in the field of physiology and pathology came with the demonstration of the function of the so-called ductless glands, the study of the effects of the emotions by Cannon of Harvard (1915), and more recently still, the studies of the chemistry of the nervous system, which promise to cast much further light on the subjects of neurology and human behavior. In the field of anatomy, the phrenological theories of Gall and Spurzheim (1830) gave impetus to modern neurology, along with the epoch-making work of Cajal (1900) and his successors on the structure of the nervous system, while the genetic formulations of Mendel (1860) have been applied to some degree to psychiatric problems in recent years. More recently, too, extensive studies have been made on the sociological and anthropological factors in the development of mental disorders.

Regarding the mentally ill, the sort of abuse that was meted out to the poor victims in Bedlam continued until the time of the French Revolution, when the increasing interest in human dignity and the rights of the individual stimulated the work of Chiarugi (1793) in Florence and Pinel (1801) in Paris. In addition to setting up principles of humane care, as did also Tuke at the York Retreat in England, Chiarugi and Pinel established the fact that mental illness is a medical problem rather than a theological or philosophical one. It was Pinel who urged what is known as moral treatment, that is, the application of pleasant surroundings and of kindly humane care, and the use of baths for sedation rather than extensive drugging.

Psychiatry, however, as we know it today, is much more recent than that. It started with Kraepelin (1883), the great German classifier, whose work was amplified by Bleuler and Jung, these latter developing their work on the findings of Sigmund Freud (1895), who in turn had been influenced by Charcot. It was Freud who gave us for the first time a true understanding of the dynamic power of the unconscious, and thus shed much light on the understanding of what the mental patient is attempting to express. It was he too who developed what is now known as psychoanalysis, an important method of psychotherapy, the basic principles of which have

permeated in large measure the whole of psychiatry. Freud's work has been even more productive in the treatment of the neuroses, which formerly were as much a *terra incognita* as the psychoses and which were recognized as treatable much later than were the more obvious mental disorders. What is known today as hysteria (in Shakespeare's time as the "mother") and the other neuroses, earlier referred to as the "vapors" for example, are, thanks to Freud, understood and treatable.

In this country psychiatry owes much to the work of Adolf Meyer of Baltimore and to William A. White of Washington, who emphasized the unity of the organism and the close interrelatedness of what we choose to differentiate as mental and somatic. Parallel with the development of psychiatry we have had that of psychology, starting with the experimental psychology of Wundt 100 years ago and developing into the many-faceted specialty of today. Of particular interest in that field is the displacement of the earlier faculty psychology by the recognition today that mental processes are integrated and that the reason is not independent of the emotions, and indeed, that much that passes for reasoning is emotionally motivated.

In the development of psychiatry the pendulum has swung to and fro, from the physical to the psychological and back, in terms both of explanation and of treatment. For many years after Shakespeare, mental peculiarities were looked on as basically physical; then, with the later rise of psychology, emphasis was laid on the psychological aspects. That there are many types of mental disturbance with an organic basis is being called to our attention lately with the growing proportion of the elderly in our population. More recently there has been a growing interest in the chemical aspects, and much is being learned from the study of the so-called ataractic drugs and of the hallucinogenic substances that produce mental symptoms closely mimicking the classical types of certain psychoses. As psychology and psychiatry have developed, they have extended beyond the private practice of clinical psychiatry into other fields such as industry, education, and the law.

In treatment, substantial progress has been made; one of the most startling triumphs has been the cure of general paresis with malaria and later with penicillin. The newer drugs, too, have been valuable aids to other forms of treatment of the psychoses, such as individual and group psychotherapy; the value of psychotherapy in the neuroses has already been mentioned. With earlier recognition and treatment, and with the growing public understanding and sympathy, the outlook for improvement and cure of mental disorders has been substantially brightened.

There are still, however, many gaps in our knowledge. The relatively recent recognition of this fact by legislative bodies and private foundations has led to the allocation of large sums of money for the support of research into the various aspects — pathological, psychological, social, genetic, and economic — of causation, prevention, and treatment. We may safely expect in the near future great advances along these lines. Psychiatry has come far since Shakespeare's day, but the road ahead is still long.

BIBLIOGRAPHY

1. Willis, R., translator. Works of William Harvey, M.D., London, Sydenham Society, 1847, p. lxiii.
2. Mercier, C. A. Astrology in Medicine, London, Macmillan, 1914.

3. Camden, C., Jr.: Elizabethan astrological medicine, Ann. Med. Hist., n. s. 2:217, March, 1930.
4. Skeat, W. W., editor: Student's Chaucer, Tale of the man of Lawe, New York, Oxford Press, 1894, p. 478, ll. 194–203.
5. Vicary, T.: True Anatomie of the Man's Bodie, London, 1587.
6. Dariot, C.: Astrologicall Judgement of the Starres, London, 1598.
7. Dell, F., and Jordan-Smith, P., editors: Anatomy of Melancholy, New York, Farrar & Rinehart, 1927, p. 180.
8. Browne, T.: Pseudodoxia Epidemica, London, 1646, book IV, chap. 13, p. 231.
9. Boorde, A.: Breviary of Healthe, London, 1552, folio 73.
10. Wedel, T. O.: The Medieval Attitude toward Astrology, New Haven, Yale University Press, 1920.
11. Kittredge, G. L.: Witchcraft in Old and New England, Cambridge, Mass., Harvard University Press, 1929.
12. Kittredge, G. L.: Notes on witchcraft, Proc. Am. Antiq. Soc., n. s. *18*:148–212, 1907.
13. Hole, C.: Witchcraft in England, New York, Scribner, 1947.
14. Zilboorg, G.: The Medical Man and the Witch during the Renaissance, Baltimore, Johns Hopkins Press, 1935.
15. Ewen, C. L'Estrange: Witch Hunting and Witch Trials, Home Circuit 1559–1736, London, K. Paul Trench, Trubner & Co., 1929.
16. Spalding, T. A.: Elizabethan Demonology, London, Chatto & Windus, 1880.
17. Castiglioni, A.: Adventures of the Mind, New York, Alfred A. Knopf, 1946, part III.
18. Notestein, W.: History of Witchcraft in England, 1558–1718, Washington, D. C., American Historical Association, 1911.
19. Glanvil, J.: Sadducismus Triumphatus, or Full and Plain Evidence Concerning Witches and Apparitions, London, 1681, part II, p. 4.
20. Wright, L. B.: Middle Class Culture in Elizabethan England, Chapel Hill, N. C., University of North Carolina Press, 1935, p. 592.
21. Cobbett's State Trials, London, R. Bagshaw, 1810, vol. VI, p. 647.
22. Demonology, London, 1597, p. 47.
23. Weyer, J.: De Praestigiis daemonum, Basel, 1563.
24. Scot, R.: Discovery of Witchcraft, London, 1584.
25. Browne, T.: Religio Medici, ed. 4, London, 1656, sect. 30, p. 64.
26. Summers, M., translator: Malleus Maleficarum, London, John Rodker, 1928.
27. Cotta, J.: The Triall of Witchcraft, London, 1616.
28. Bekker, B.: The World Bewitched (translated from the Dutch), London, 1695.
29. Webster, J.: The Displaying of Supposed Witchcraft, London, 1677.
30. Hutchinson, F.: Historical Essay on Witchcraft, London, 1720.
31. Singer, C.: Short History of Medicine, Oxford, Oxford University Press, 1928.
32. Lemnius, L.: Preservation of Health, London, 1576, p. 89.
33. Osler, W.: Yale Rev., n. s. 3:251, 1914.
34. Walkington, T.: The Optick Glasse of Humours, London, 1607, chap. 12.
35. Du Laurens, A.: A discourse of the Preservation of the Sight: of Diseases of Melancholy: of Rheumes and of Old Age, translated by R. Surphlet, London, 1599, p. 85.
36. Huarte, J.: Examen de Ingenios, or The Tryall of Wits, translated by Bellamy, London, 1698.
37. Barb, L.: The Elizabethan Malady, Ann Arbor, Michigan State College Press, 1951.
38. Batman upon Bartholome: De Proprietatibus Rerum, London, 1582, p. 89.
39. Bright, T.: Treatise of Melancholy, ed. 2, London, 1613, p. 319.
40. Dickson, S. A.: Tobacco—Panacea or Precious Bane, New York, New York Public Library, 1954, p. 162.
41. Gerard, J.: The Herball, London, 1597.
42. O'Donoghue, E. G.: The Story of Bethlehem Hospital from its Foundation in 1247, New York, E. P. Dutton Co., 1915, pp. 168, 107.
43. Lavater, L.: Of Ghostes and Spirites Walking by Nyght, London, 1572, p. 13.
44. Percy, T., editor: Reliques of Ancient English Poetry, ed. 3, London, 1775, vol. 2, p. 351.
45. Auden, W. H., editor: Oxford Book of Light Verse, London, Oxford University Press, 1938, p. 112.

Friends for the Road*

Félix Martí-Ibáñez, M.D.

PROFESSOR AND DIRECTOR, DEPARTMENT OF THE HISTORY OF MEDICINE,
NEW YORK MEDICAL COLLEGE, FLOWER AND FIFTH AVENUE HOSPITALS;
EDITOR-IN-CHIEF OF MD MEDICAL NEWSMAGAZINE
NEW YORK, N. Y.

In these summer days of golden leisure, when there is a little more time for reading, let us talk about books.

Charles Grosvenor Osgood once suggested that the best way to withstand the stresses of modern life was to select a great poet as constant guide and companion in the daily adventure of living—a poet who would be an angel forever hovering at our shoulder, a Vergil capable of transporting us to the paradise where Beatrice waited for Dante. Such a poet had to be a source of inspiration, a teacher, a synthesis of intellect and spirit, humaneness and encyclopedism.

Years before I read Osgood's advice, I had already "adopted" several authors—Cervantes, Ortega y Gasset, Montaigne, Goethe, Dickens, Romain Rolland, Vivekananda, and others—as faithful companions on the road of life. My choice was guided by the affinity I felt toward these men and by the conviction that their minds were vast regions to be endlessly and passionately explored. For the spiritual reward in reading again and again the authors of one's choice is that one keeps on discovering new values in them, just as he who devotes himself to knowing one city alone keeps on discovering new attractions that are missed by the globetrotter, who knows the world with the same skin-deep superficiality with which Don Juan knew his women, while their inner beauty completely escaped him.

But here I wish only to answer a question put to me by some colleagues. Which ten *recreational* books would I take with me on a vacation? The question is irresistible, for books are the tapestry with which I have decorated my spirit.

I shall begin by eliminating all recent books, bearing in mind Emerson's counsel not to read a book less than a year old. Where choice is of the essence, it is well to heed such advice. Besides, most of the latest literature is ephemeral and deserves no more attention than any common pastime. Most "best-sellers" are forgotten as soon as they become outmoded. For of all the fashions, the most old-fashioned, in literature as in clothes, are not those that are centuries old but those of yesterday.

The first book I would select would be that inseparable companion of my life, *Don Quixote*. As a child they made me detest it in school, just as children in schools here learn to detest Shakespeare. How fortunate I was to rediscover it later! For *Don Quixote* is a perennial garden, each page abloom with gorgeous flowers. It is Aladdin's cave overflowing with priceless treasures. It is perhaps the greatest novel ever written and no other book has exerted so much influence on human ideals. One is at once amused and touched by the adventures of the romantic knight who, mad in mind and pure in thought, sought to transfigure, before reforming it, the

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world, and one also takes great delight in the style, of biblical simplicity. This is a human comedy, a vast landscape drenched in the sun of life, peopled by beings rich in color and drama. Every year I reread *Don Quixote*, and my soul gains moral weight and is enriched with ounces of sunlight.

Next is Montaigne's *Essays*. A pirates' coffer could hold no greater variety of unexpected treasures. Sitting by the fire in his castle, the author, shaking with cold, finds warmth in his own thoughts. He is not gentle and kind like Cervantes, but he is wise and understanding. His work, like a *poularde au demi-deuil*, is encrusted with savory truffles—anecdotes, commentaries, ironies, witticisms, and wise sayings—and his prose has a sober musicality.

To nourish the yearning to travel in time instead of space, I would choose the two best historical novels I have ever read: *The Cloister and the Hearth*, by Charles Reade, and *The Romance of Leonardo da Vinci*, by Dmitri Merezhkovski. This preference compels me to pass up with much regret Dumas' musketeers, for while I can hardly think of a more delightful friend than D'Artagnan in *Twenty Years After* and the *Viscount of Bragelonne* (a feeling shared by Robert Louis Stevenson), in historical value and literary style Dumas' books cannot compete with the two novels mentioned.

The Cloister and the Hearth was called by our famous colleague, Arthur Conan Doyle, "the greatest English novel." Let Dr. Conan Doyle tell himself what Charles Reade did:

> He takes the reader by the hand, and he leads him away into the Middle Ages, and not a conventional study-built Middle Age, but a period quivering with life, full of folk who are as human and real as a bus-load in Oxford Street. He takes him through Holland, he shows him the painters, the dykes, the life. He leads him down the long line of the Rhine, the spinal marrow of Medieval Europe. He shows him the dawn of printing, the beginnings of freedom, the life of the great mercantile cities of South Germany, the state of Italy, the artist-life of Rome, the monastic institutions on the eve of the Reformation. And all this between the covers of one book, so naturally introduced, too, and told with such vividness and spirit. Apart from the huge scope of it, the mere study of Gerard's own nature, his rise, his fall, his regeneration, the whole pitiable tragedy at the end, make the book a great one. It contains, I think, a blending of knowledge with imagination, which makes it stand alone in our literature.

Little more could be added to this brilliant description made by Conan Doyle in his *Through the Magic Door*, a piece of writing itself as precious as a rare gem and, unfortunately, as little known as many of the Amazon's mysterious tributaries.

Merezhkovski's *The Romance of Leonardo da Vinci* could easily make today's historical best-sellers blush with shame. Its pages sparkle and glitter with the robust polychrome world of the Renaissance. Not only da Vinci but his times spring to life in this vivid portrayal of the most extraordinary period in history, when, after the long medieval night, a brilliant rainbowed dawn heralded a wondrous new world. In my opinion, these two novels are superior even to Tolstoi's *War and Peace*, another formidable contender.

From a man of encyclopedic knowledge like Leonardo, let us turn to a man encyclopedic in love: Giovanni Jacopo Casanova. Do not be alarmed, but I consider Casanova's *Memoirs* (not the cheap abridged editions, but the great eight-volume

French edition of which there is an excellent English translation) one of the most dazzling paintings of his times and a fascinating portrait of a unique man, as devoted to collecting women as an entomologist is to collecting bugs. Written in beautiful terse French, the *Memoirs* reveal extraordinary descriptive powers. Characters and scenes succeed one another in a Mardi Gras crescendo. It is interesting to observe that the landscape did not exist for Casanova. Strictly a man of action, he devoted numerous pages to describing in detail one single amorous encounter, while dismissing in a few words the lovely cities that sheltered his love affairs. The *Memoirs* are a human document of extraordinary interest from a psychopathological viewpoint. To physicians they represent, besides, a window opened wide to the medicine — the great physicians and the quacks, Casanova among them — of the eighteenth century.

From the diabolical to the angelical. A physician who never became famous as such but who gained immortality as an author, Dr. Oliver Goldsmith wrote *The Vicar of Wakefield*, which Goethe considered the greatest novel of the eighteenth century and which Dickens took to bed and reread every night. Goldsmith studied medicine in Edinburgh and Padua, but he failed professionally in England and died owing 2000 pounds. *The Vicar of Wakefield*, his most famous novel, which moved Walter Scott to say: "We read it in youth and age, we return to it again and again," and Samuel Johnson: "Goldsmith writes like an angel," is the biography of a pure kind man. Through its pages there flows a stream of limpid, graceful prose, charm, and humor. Upon reading such pages one's soul becomes decked with sweetness and tenderness.

A sister to this last novel in the purity, simplicity, and generosity of the hero is the *Pickwick Papers*, by Charles Dickens. This book sings and dances. Its pages ring with the clangor of hunting horns and the jingle of bells on stagecoach mules. No other novel illustrates so well the fact that our predecessors walked when they strolled and ran when they wrote, whereas today we run when we stroll and we creep when we write. The *Pickwick Papers* are all action and enterprise steeped in tender sentimentalism and sharp humor. The world in this book, sun-sparkled and gay, teeming with stagecoaches jogging along frosted roads, inns with blazing fireplaces, storybook Christmases, and romantic loves — this world of Dickens is an eiderdown quilt to warm all cold hearts.

A beautiful contrast to this last book is Voltaire's *Candide*, which describes the adventures of a young man who travels the world in search of love, fortune, and the meaning of life. *Candide*'s greatest charms are its profound satire on the philosophy that we live "in the best of worlds" and its magnificent crystalline prose. Read *Candide* if you crave to write with diaphanous clarity. Its pages vibrate with lights and shadows, with subtle sensualities and poignant yearnings.

An altogether different hero is that of *Jean Christophe*, by Romain Rolland, published in French in ten volumes and in English in one volume. Originally, Romain Rolland intended to write the life story of Beethoven, but he ended by writing a masterpiece wherein is resumed the author's life creed as action and service. This is the book, together with *The Universal Gospel* by the same author, that has most influenced my life. *Jean Christophe* is a symphony of words and the bible of humanity. Here is

a universal message (completed in the author's other novel, *The Enchanted Soul*) symbolized in a river, on whose banks the hero dreamed as a child.

Source of mental peace, inspiration, and beauty—such is Thoreau's *Walden*, another faithful companion of many years. In this sensitive book we can live step by step the author's voluntary exile at Walden Pond, witness and feel the change of seasons in his Robinsonian isolation: the silver petals of the snow silently drifting to the ground, the quiet clamor of spring bursting into tiny green tendrils and shy many-hued blossoms, the glowing fires of autumn, the summer's golden peace; and, enveloped in the fresh aromas imprisoned between the pages, we can listen to the stirring inner music of the author, who finally found peace facing the placid waters of Walden Pond.

I should be most happy if I could top this delectable parfait of ten great books with the eleven adventures of John Buchan's hero, Richard Hannay; John Steinbeck's stories of the *paisanos* of Monterey; the historical novels of Conan Doyle; the great major novels of R. L. Stevenson; and my two favorite and often read novels by the physician-author, W. Somerset Maugham, *Cakes and Ale*, a technical masterpiece, and *The Narrow Corner*, a marvelous narrative.

But as Conan Doyle would say, the moment has come to close the magic door to the library and open another door far more magical: the cover to any of these books, all of them passports to the paradise of reading, the most beautiful, peaceful, and eternal of all paradises.

Course in Rehabilitation Care of the Chronically Ill Patient

A one-week course for physicians, devoted to the rehabilitation care of the chronically ill patient, will be held Nov. 16–20, 1959, under the auspices of the Department of Physical Medicine and Rehabilitation, New York Medical College–Metropolitan Hospital Center, New York City. The course will offer a review of the principles and techniques in the medical care of the chronically ill to meet the needs of the clinician, medical administrator, and public health physician. The course will include: physiology and pathology of chronic diseases, nutrition and dental care, management of bedridden and incontinent patients, home care programming, community needs and resources, public health aspects, self-care activities, prosthetic devices, and psychological and social aspects.

The tuition fee is $100.00. Traineeships for tuition, maintenance, and travel are available through funds provided by the U. S. Office of Vocational Rehabilitation. Applications for the course and traineeships can be obtained directly from Dr. Jerome S. Tobis, Chairman, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 East 105th Street, New York 29, New York.

BOOK REVIEWS

On the Trail of the Poltergeist. NANDOR FODOR. New York, The Citadel Press, 1958. Pp. 223. Price $3.95.

Ghosts haunt houses at night, poltergeists haunt people in daylight. In lore and literature the "life cycle" of a ghost is usually a long one, while a poltergeist's is short—though merry and mischievous—a few weeks or months at the most. A "racketing spirit" or poltergeist, twenty years ago, terrorized the dignified suburban home in Thornton Heath, England, of Mr. and Mrs. L. Forbes, who lived with their son David and a crippled lodger. Objects vanished, crockery broke, stones were thrown, saucers flew, and noises of a "psychic" origin were heard. The phenomena centered around lively Mrs. Forbes. Roman lamps and a prehistoric flint axe suddenly sprang out of nowhere before her eyes, a Byzantine necklace was placed around her neck by invisible hands, and she was clawed by an invisible tiger.

Dr. Fodor, in an attempt to explain the case, investigated the phenomena and eventually traced them to the unconscious mind of Mrs. Forbes and to her sexual neurosis and childhood traumas. The tale of how the author studied the case makes fascinating reading and confirms his reputation as one of the foremost scientific investigators of "psychic" phenomena. This is a lively book, which in manuscript form was read and praised by Freud.

Poltergeist phenomena, according to Dr. Fodor, are an episodic mental aberration of a schizophrenic character arising from mental trauma and subsequent dissociation. Mediumistic apports are produced as a neurotic develops his symptoms and may actually be a kind of self-therapy. To Dr. Fodor, the origin of poltergeist psychoses may be a sort of psychic lobotomy, and explosive cleavage of the personality, which tears away and lets loose, floating free, an infantile fragment of the psyche, which then proceeds to raise hell around the poltergeist progenitor, just as a wicked child might do to a harassed parent. *Félix Martí-Ibáñez, M.D.*

Practical Leads to Puzzling Diagnoses. WALTER C. ALVAREZ. Philadelphia, J. B. Lippincott Co., 1958. Pp. 490. Price $9.00.

Walter C. Alvarez has been for many happy years not only a great physician in the noble sydenhamian tradition, but also a great educator endowed with boerhaavian *savoir faire* and oslerian *savoir dire*. His books, like his lectures and his conversations, are always challenging, enlightening, and practical. He has imagination and definite opinions, and makes the best of them for the good of his colleagues and his patients. He hides his erudition under a mantle of humor, his clinical vision under a cloak of common sense, perhaps the greatest of his many medical virtues. To read his books is always an education and a delight, even for those who might not agree with him.

And now, once again Walter C. Alvarez returns to one of his basic preoccupations the little things in the clinic that conceal enormous medical problems. This time it is not the "little strokes," which he has studied so brilliantly in the past, but the little symptoms behind whose flimsy covering lies the ominous façade of psychoses. Digging into his experience of half a century with patients, he has thrown to the

arena the challenging question of the families of patients afflicted with epilepsy, alcoholism, psychosis, or other mental disease. He has found that in this country millions of relatives of the institutionalized, hospitalized, and undiagnosed ambulatory mental patients have themselves an appalling variety of mild symptoms of psychoses, hidden under the disguise of countless clinical diagnoses. He is puzzled by the patients with a so-called organic disease, which might be nothing else but a neurosis or a mild psychosis. And he does what a true physician should do. He goes back to that precious reservoir of medical knowledge—the archives in which are classified hundreds of clinical case histories, and he collects data on *relatives* of alcoholic, epileptic, and psychotic patients.

Remembering that classic authors already recognized the major equivalents of mental disease, Dr. Alvarez looks for the *minor* equivalents. He investigates all the strange symptoms and syndromes present in millions of persons (exemplified by the hundreds of case histories collected by him) who are considered "organic" patients and who go to an internist, and discovers that often these patients' organic disease is of no great significance and is *not* really producing their currently disturbing symptoms. He looks into heredity factors (which he considers the most important) and environmental conditions, and peers into carriers of psychoses who seem to be normal and "sane."

The result of this vast undertaking is a monumental book describing the symptoms and syndromes that he found were bothering 574 relatives of psychotics and alcoholics and 99 relatives of epileptics. And he concludes that of the "nervous" and neurotic persons seen daily by general practitioners and internists, about 90 per cent are neurotics amenable to psychotherapy and the rest are "eccentric and poorly adjusted persons who suffer fear, phobias, compulsions, mild depressions, and other symptoms," which he accepts as revealing of psychosis.

This book, because of its clinical scope, defies reviewing, but richly deserves to be read by practicing physicians who encounter these problems daily. It is written in the unique Alvarez style—terse, plain, and hard hitting, with Mediterranean luminosity, and the deftly selected literary and medical quotations are like the savory truffles in a succulent pie.—*Félix Martí-Ibáñez, M.D.*

Mechanisms of Hypertension: With a Consideration of Atherosclerosis. HENRY ALFRED SCHROEDER, M.D. Springfield, Ill., Charles C. Thomas, 1957. Pp. 379. Price $9.00.

The basic mechanisms of hypertension are examined in this book with an attempt to relate them to laboratory and clinical evidence. The author discusses: the complex of factors in the human disease, basic or constitutional factors, neurogenic and nephrogenic effector mechanisms, factors influencing the conversion of neurogenic to nephrogenic hypertension, trace metals and cardiovascular disease, mechanisms in atherosclerosis.

Therapy of hypertension and atherosclerosis are discussed less thoroughly.

The book is well organized and well written and it includes a helpful bibliography and index.

Technique of Fluid Balance: Principles and Management of Water and Electrolyte Therapy. GEOFFREY H. TOVEY, M.D. Springfield, Ill., Charles C. Thomas, 1957. Pp. 100. Price $2.50.

This brief monograph is a succinct outline of factors in body fluid equilibrium and techniques for correction of fluid imbalance. Pointing out that water and electrolyte therapy must often be carried out in the absence of any laboratory aids, the author includes a helpful appendix of rapid and simple chemical techniques for use when full laboratory facilities are not available.

Chapters are included on: volume, distribution, and chemical composition of body fluids, physiology of fluid balance, consequences of fluid depletion, maintenance of fluid balance, diagnosis and treatment of body fluid deficit, adverse effects of treatment, special problems, technique.

The Principles of Therapeutics. J. HAROLD BURN, M.A., M.D., F.R.S. Springfield, Ill., Charles C. Thomas, 1957. Pp. 278. Price $5.50.

Although titled *The Principles of Therapeutics*, this book actually deals as much with pharmacology as with therapeutics. Most of its 33 chapters consider particular drugs and groups of drugs, e.g., analgesic substances, alcohol, anesthetics, stimulants, insulin, metallic salts and vitamins.

This book is not recommended as textbook or physician's reference because it contains several inaccuracies and half-truths—for example, chloramphenicol is used for a broad range of conditions, although the author advises that it be used only for typhoid fever. The bibliography is inadequate, and in addition to the inaccuracies, in many cases the discussion is not very thorough.

Essentials of Human Reproduction: Clinical Aspects, Normal and Abnormal. EDITED BY JOSEPH THOMAS VELARDO. New York, Oxford University Press, 1958. Pp. 270. Price $13.50.

A carefully written, well-organized review of essentials of human reproduction is to be found in the 10 chapters of this book, each written by one or two prominent specialists in clinical endocrinology. A study of endocrines and reproduction is presented first, followed by a description of ovulation, menstruation, and aspects of pregnancy. Disturbances of pregnancy, gynecological disorders, infertility, and endocrine pathology of female and male reproductive systems are considered next.

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Associate in Ophthalmology
Medical College of Virginia, Richmond, Virginia

Foreword by FELIX MARTI-IBAÑEZ, M.D.

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